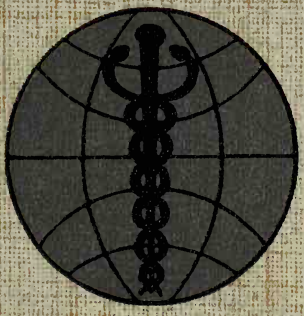
THE MEDICAL CLINICS OF NORTH AMERICA



SYPHILIS AND OTHER VENEREAL DISEASES

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THE MEDICAL CLINICS OF NORTH AMERICA

SYPHILIS AND OTHER VENEREAL DISEASES

A Symposium in Honor of
Rudolph H. Kampmeier

JOHN B. YOUMANS, M.D.
Guest Editor

Volume 48 — Number 3
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SPECIAL DISTRIBUTION OF THIS ISSUE

At the request of the United States Public Health Service, the publishers have agreed to make available to Health Departments extra copies of this issue for presentation to selected physicians in the United States. The Public Health Service feels that the information contained in this symposium is of vital importance to national health and that its distribution should not be restricted solely to subscribers to the Medical Clinics.

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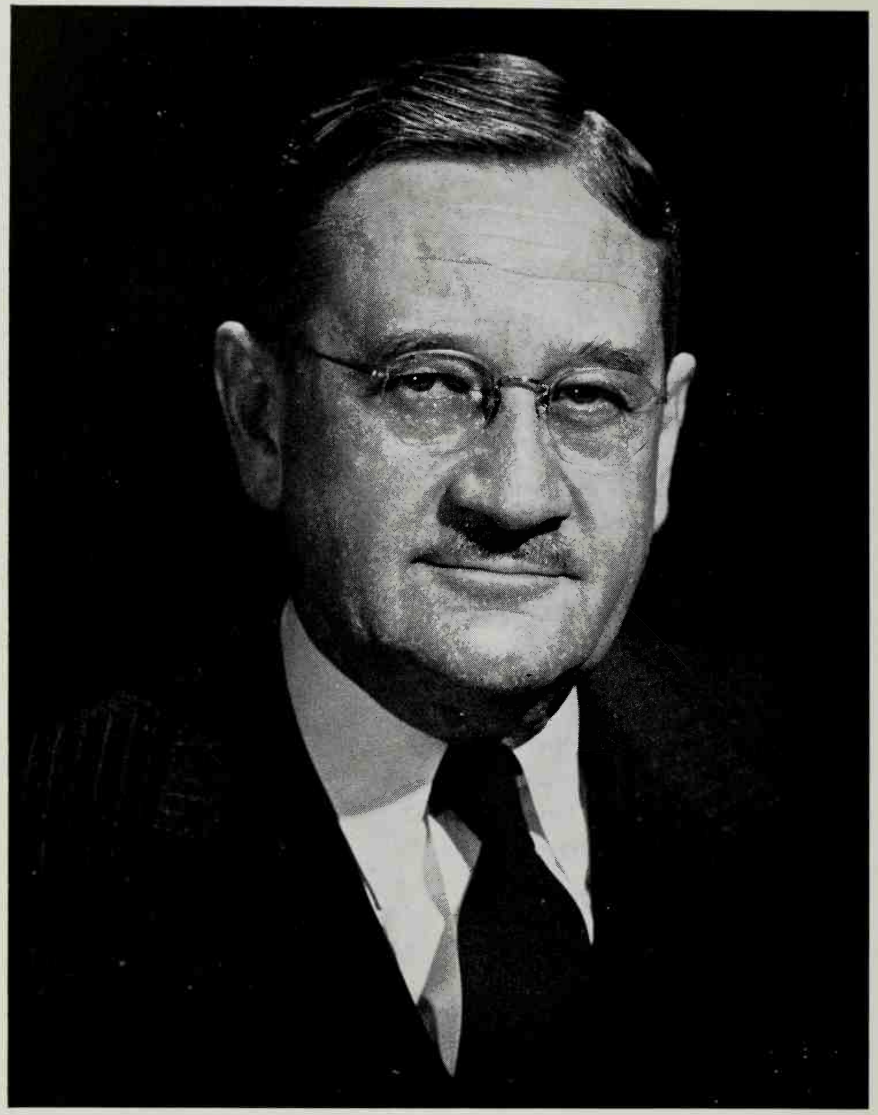

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SYMPOSIUM ON SYPHILIS AND OTHER VENEREAL DISEASES

Dedicatory Foreword

In a period in medicine when highly sophisticated and complex procedures have supplemented and indeed supplanted much of the personal detection, identification and evaluation of the manifestations and mechanisms of disease, those due to pathogenic micro-organisms remain a group less affected than others. Among these, syphilis is the captain. In no other disease does the need for acute and accurate observation by the use of the five senses for the detection of physical signs and symptoms, for their interpretation and evaluation, for the information obtained from the patient and a limited variety of laboratory tests, all supported by inductive and deductive reasoning based on experience, play so great a part in diagnosis, in prognosis and in judgment as to treatment.

It is eminently fitting, therefore, that this volume of collected papers dealing with syphilis and other venereal diseases, themselves in many instances both historically and at present complicating the diagnosis and management of the great pox, should be dedicated, as was the symposium on which it was based, to Dr. R. H. Kampmeier. An accomplished diagnostitian, a consummate clinician, an inspiring teacher and a distinguished editorialist, as a syphilologist he deservedly ranks with the most distinguished physicians in the field in modern times. Nor is this all. By its very nature, by its demoniac versatility and mimicry, syphilis demands for competence in its diagnosis and management a corresponding competence in the whole field of internal medicine. Indeed, it is to an eminent internist and teacher, a distinguished physician of physicians that this volume is a highly deserved, if inadequate, tribute.

JOHN B. YOUMANS, M.D.
Guest Editor

2 East 103rd Street
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Role of Public Health and Private Medicine in the Eradication of Syphilis

WILLIAM J. BROWN, M.D.*

I don't believe that there is any one in this audience who does not respect both truth and logic. Therefore, because the subject which I am about to discuss is both of great importance and great urgency, I hope you will permit me to be both frank and analytical. And I hope you will accept what I have to say in the spirit in which I say it.

It is not my intention to be critical, but rather to explore realistically the problems surrounding the epidemiology of syphilis, problems of great concern to both public health and private medicine.

I don't know how many of you read the editorial entitled "Why the Increasing Incidence of Syphilis?" in the March 30, 1963 issue of the *Journal of the American Medical Association.* Those of you who did may remember that it asked the following questions:

"Why, in 1963, has there been a sudden reawakening of interest in a disease which had seemed more or less forgotten? What is the urgency which surrounds syphilis and its control?" Let's think about this for a few minutes.

Once Syphilis Ravaged Nations

Syphilis, I suppose, is as old as man himself; or almost as old anyway. It has been considered one of the great plagues of mankind. At least once in recorded history, it swept an entire continent in a relatively short time, killing literally millions of persons, and crippling millions more. In fact, smallpox, which today we consider not only frightening, but absolutely intolerable down to the last single case, was named in contrast to a then much more formidable disease; and that disease was, of course, the great pox—or, as we call it now, "syphilis."

Read at, Syphilis: A Symposium, Vanderbilt University School of Medicine, Nashville, Tennessee, May 17–18, 1963.

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Actually, although the treponeme seems to have become somewhat less virulent after the eighteenth century, syphilis continued to do a fantastic amount of damage right down through a good part of the twentieth century.

Then Came Penicillin, Quick Office Cures and De-emphasis

Penicillin, of course, was introduced into syphilotherapy in the 40's with such dramatic results that it was considered by many to be the so-called "breakthrough" that mankind had been working toward and hoping for for centuries; and all over the country, people who probably should have known better hailed the eradication of syphilis as a foregone conclusion. The statistics seemed to bear out this thesis, because infectious syphilis dropped from a 1947 high of more than 100,000 reported cases to a low of 6516 cases in 1955, and congenital and late manifestations receded similarly.

Nineteen hundred fifty-five was the year that the late Paul O'Leary, one of the leading dermatologists of his time, summed up the attitude of the medical profession generally when he dropped the phrase "and Syphilology" from the "A.M.A. Archives of Dermatology and Syphilology," of which he was editor.

Syphilology was also de-emphasized in the curricula of medical schools throughout the country; and thousands of young doctors came to graduation without ever having probed the depths of the meaning behind Sir William Osler's famous predication that: "To know syphilis is to know medicine."

The Board of Commissioners of the Joint Commission on Accreditation of Hospitals dropped routine admission serologic tests for syphilis as a requirement for hospital accreditation on January 28, 1956; and many authorities began to proclaim the required premarital blood test a useless relic.

Federal venereal disease control appropriations, which had exceeded $17,000,000 annually, also were reduced in 1955 to a low of $3,000,000. (Although I might add that we were spending at least ten times that much on institutional care of paretics, and in fact, still are.) At the same time, state and local appropriations for venereal disease control dropped almost out of sight.

The Rude Awakening

There were some who were not totally enchanted by the promise of penicillin. Early in 1956, the Joint Statement of the Association of State and Territorial Health Officers, the American Venereal Disease Association, and the American Social Health Association took the general overoptimism to task and, although that was the year when reported infectious syphilis had reached its lowest level, this group hinted strongly that the trend might not continue. And they were proved right.

In 1957, 6250 cases of infectious syphilis were reported. Six thousand six hundred were reported in 1958; 8100 in 1959; and so on, until in 1962 more than 20,000 cases were reported.

Private Patients Were Lost to Epidemiologic Study

Now I want to go back and quote the J.A.M.A. editorial to which I alluded earlier, because I believe it makes a very valid assertion. It said this:

"The successful control of syphilis between 1936 and 1946 . . . was the result of treatment of acute syphilis in public and university clinic hospitals, application of epidemiologic methods to investigation of contacts, case-finding, widespread serologic testing, etc. . . . (I'm still quoting) Up until 1946, the financial burden of prolonged chemotherapy, and the attendant inconveniences, technical difficulties, and complications led to mass treatment in public clinics and *little in the private physician's office*" (in other words, to paraphrase this, treatment and follow-up of syphilis at that time was so troublesome that the average private physician didn't want to bother with it, so he channeled most of the syphilis patients to public health facilities, where they were not only treated, but followed, and also interviewed thoroughly for their contacts. The editorial continues) "but when penicillin became generally available, its ease of administration and need for few injections moved the treatment into the hands of the practicing physician and his office nurse . . . (and I'm still quoting) Therefore, it may be said that, as the patient moved into the physician's office for treatment, he was lost to epidemiologic control or case-finding" (end of quote).

Actually, for a while, however, most of us in public health did not fully comprehend the significance of the phenomenon which is described here.

It *is* true that as reported cases of infectious syphilis began to increase, particularly in the lower age brackets, and in the upper classes of society, control *appropriations* also came to be increased, with the result that badly depleted public health staffs were supplemented with new people of the highest quality obtainable from colleges and universities throughout the country, and additionally trained in the latest techniques of venereal disease epidemiology. And so, the full light of modern epidemiology was thrown on almost all the cases treated in public clinics.

Public health people, however, were aware that a number, and perhaps a large number of infected persons were being treated privately, and that few of these were being interviewed adequately for contacts; but many felt, for a long time, that a sufficient percentage might somehow be brought into public clinics so that the number lost to epidemiology would be insignificant to the total picture.

But it took most of us a long time to comprehend fully that, for a number of reasons, we were living in a fool's paradise. The truth was that we were doing little more than scratching the surface of epidemiology. To

say that many infected persons were slipping through the epidemiologic net is to make a gross understatement. It is hardly an exaggeration to say that *most* were.

What were some of the reasons for this? Well, for one thing, a generation of physicians had gone into private practice, most of whom, for the reasons previously mentioned, had never seen a syphilitic lesion. And 7000 more were, and are, being graduated annually who have never been exposed to more than a scant few hours of syphilology. That they were not prepared for syphilis was not their fault. In fact, the blame could not be laid on anybody's doorstep. It was simply a phenomenon of the times. Nevertheless, to literally thousands of these physicians came literally thousands of syphilitics—but quietly and covertly, a case here and there, because indiscriminate sexual behavior is seldom accompanied by fanfare.

With what results?

In many cases, syphilis was not deliberately *excluded* from differential diagnosis; it was just *not even considered as a possibility;* and the case was often diagnosed as an allergy or some other benign dermatosis, and was treated accordingly.

Moreover, in many cases, when a reactive serologic test for syphilis was discovered by one means or another, there was often a tendency to interpret the serology as a biologic false-positive reaction. In such cases, even if "insurance" therapy was administered, the patient usually was lost to epidemiology.

This situation was not, of course, etiologically responsible for the continuing increase of syphilis; but gradually, it became apparent to many persons in public health that, as long as it continued, there was little hope for the control of the disease, to say nothing of eradication.

Recognition of the Need for Cooperation Between Public Health and Private Medicine

Representatives of health departments around the country began to follow up reports of infectious syphilis morbidity, asking whether the patient had had an epidemiologic work-up, and if not whether a health department epidemiologist might have the physician's permission to do one. And to the surprise of many skeptics, such permission was often granted.

Then a number of health departments—first a few, then many—began to check reactive laboratory reports with the submitting physician to inquire whether a diagnosis had been made, and whether the case had been reported. The success of all this activity is indicated by the following:

Between 1959 and 1962 the number of individual private physicians reporting primary and secondary syphilis throughout the country increased by 75 per cent; and the total of private physicians reporting cases in 1962 numbered about 3900.

Over the same period, of the total cases actually reported, 50 per cent

were interviewed for contacts in 1959 and this figure increased to 81 per cent in 1962.

Moreover, with respect to the thoroughness of the interview, of those interviewed in 1959, only 41.4 per cent were seen by the interviewer more than once; but in 1962, 70.9 per cent of these private patients were seen on two or more occasions by the interviewing epidemiologist. The results of this improvement are reflected in the fact that in 1959 only 30.6 per cent of these private patients disclosed either the source of their infection or someone to whom they transmitted it. By 1962, this figure had risen to 53.2 per cent.

In fact, the value of this kind of cooperation was demonstrated so conclusively that the Surgeon General's Special Task Force last year was convinced that, if the same kind of activity was carried out universally, along with a suitable public and professional education program, it might be entirely possible to eradicate syphilis.

Recognizing, however, that a much more accurate index of the actual incidence of syphilis was needed, the American Medical Association, the National Medical Association and the American Osteopathic Association all cooperated with the American Social Health Association in a joint nationwide morbidity survey, the results of which were released in April, 1963.

They queried 183,000 physicians in all, and received an astounding response from 131,000. Probably the most important finding was that, for every privately treated case of infectious syphilis identified and reported, approximately nine cases had been identified and treated privately and *not* reported. This means that while in 1962, 20,000 cases of infectious syphilis were reported, of which the techniques of epidemiology were applied to about 16 or 17 thousand, the truth is that an additional 49,000 or so cases were treated privately and not reported. And, considering the annual level of reported early latent syphilis, the actual *incidence* of syphilis must now be something in excess of 120,000 cases.

Yet every case of infectious syphilis, as every case of typhoid, polio, plague or the smallpox, is important from the standpoint of eradication. To quote again from the same J.A.M.A. editorial I mentioned earlier, "In the overall control and eradication of venereal disease, treatment is hardly more than *secondary* to case-finding and investigation of contacts."

To be Eradicated, Syphilis Must be Labeled Intolerable

We have asked ourselves many times why it is that the average doctor, having found a case of typhoid, polio, plague or smallpox, almost couldn't get to the telephone fast enough to alert the Commissioner of Health. Yet, the same physician will not get excited about the presence of syphilis. And we have come to this conclusion: that infectious diseases can be sorted rather neatly into two categories: tolerable and intolerable; and that, to be eradicated, a disease must be moved into the *in*tolerable cate-

gory and stay there. Although *in*tolerable diseases are introduced into the country occasionally, they are always re-eradicated to the last trace, regardless of cost; whereas, tolerable diseases, on the other hand, are "controlled" at so-called "tolerable" levels.

In fact, we have postulated a law of public health relating to the control of tolerable diseases, to-wit: "As a disease *control* program approaches the end-point of eradication, it is the *program* rather than the disease which is the more likely to be eradicated." After that, of course, the disease simply gets out of control again and begins another cycle. And this, of course, is precisely what happened to syphilis in the mid '50's.

I wish I could tell you why certain diseases enjoy this status of intolerability while others do not. It's a thing which is difficult to pin down, but I'm sure that both public and professional education, associated ideas, public images, etc., have a lot to do with it.

Probably another important factor is that, while most influential persons have some personal fear of these other dread diseases, few will admit to themselves that they might ever contract syphilis. Perhaps it is an unfortunate thing for the eradication of syphilis that it is *not* contracted from door handles, drinking fountains and toilet seats as in popular legend. In fact, one health educator recently suggested facetiously, but with a grain of truth, that if a virulent *T. pallidum* could be demonstrated in a can of tuna fish, the eradication of syphilis might be well on its way.

We talk about dread diseases, and plague is about as dread as they come; yet if I'm not mistaken, for *every* person who died from plague in the United States last year, *1000* died from syphilis.

Perhaps you've noticed a difference in terminology about diseases. We talk about a smallpox scare, a typhoid scare, a plague scare or a polio scare, but never about a syphilis scare. We occasionally talk about a syphilis outbreak, but we seldom even go so far as to use the term syphilis epidemic. Probably one of the reasons for this is that, far from having reached a status of intolerability, syphilis has barely achieved a status even of *visibility*.

I feel that many physicians are probably still correct when they say they haven't seen a case of early syphilis in 20 years. A few physicians are seeing a considerable number of cases, but the bulk of the cases are sparsely scattered. And because of the overall public and professional attitude toward syphilis, when a case *is* encountered, there is a tendency to consider it more of a curiosity than a cause for alarm; and until recently, there has seemed to be little urgency in reporting it, or in working it up epidemiologically.

But somewhere along the line, this attitude is going to have to change; and I sincerely hope it will happen while penicillin is still effective; and how long that will be is anybody's guess.

However, I think that it can be done through education, both public and professional—that is, through mass public awareness programs—

through the introduction of material on venereal disease in grade and secondary school curricula—through the re-introduction of syphilis at appropriate places in the medical school curriculum—and through an exchange of information and discussion of venereal disease among professionals.

Education and Epidemiology Are Necessary

Quite a bit of this sort of activity is being fostered by public health people now, and I hope more will be. A number of good materials and techniques have been developed for public education; and also some very good new educational items have been made available to medical schools and professional societies, and more are on their way.

But recognizing the great need for epidemiology, a large part of venereal disease control resources available to public health are continuing to be channeled into shoe-leather epidemiology. The Public Health Service, for example, is continuing to train a large force of specialized nonmedical personnel in the techniques of syphilis epidemiology, and is making them available through state and local health departments wherever they are needed. And these are supplemented by several hundred state and local people—nurses, field workers, etc., also working full or part time in syphilis epidemiology.

But if these techniques and resources are to be effective, they will have to be put to maximum use.

The Pivot of an Eradication Program is the Doctor in Private Practice

In a separate article in the March, 1963 issue of the *Journal of the American Medical Association*, to which I referred earlier, Dr. Kampmeier wrote:

"If it is true that more patients are treated in doctors' offices than in public clinics, eradication of syphilis *must* have as its pivot the doctor in private practice, and will depend mainly upon cooperation of the practitioner with health authorities."

This argument, we now know, is unimpeachable. But there probably are a number of ways of looking at this so-called "cooperation." The suggestion usually made is that the private physician report all his cases and *allow* the public health epidemiologist to interview his patients. More often than not, this means today that, having learned of the diagnosis of an early case, a health department epidemiologist will approach the physician and seek permission to interview the patient—permission which may or may not be granted for any number of reasons.

There probably are a number of other ways epidemiology might be handled, but the fact remains that in some way, for very practical reasons, the responsibility *must be delegated* by the physician, and if this has not so far been considered by professional committees on ethics, it well might be.

While many private physicians *do* ask the patient about sexual

contacts themselves, it is not realistic to ask or expect the average physician today to spare the extra hour and often *more* of time required for a thorough probe for contacts—a probe which often extends to several sessions and often discloses a surprising number of contacts when it is conducted by a trained interviewer. And the search for these contacts, which may extend over several states and countries, definitely is beyond the scope of the busy physician. So to expect the private physician to bear the active *burden* of epidemiology is simply not realistic, although under the circumstances he must bear the moral burden.

The idea which *has* worked and worked well for several thousands of physicians is for the physician to diagnose and treat, and then call the public health epidemiologist by telephone to report the case and request him to interview the patient as soon as possible.

And where this works best, you could not say that the physician *allows* the epidemiologist to interview his patient. The fact is that many a private physician now takes the public health responsibility by the horns, so to speak, and *insists* that a qualified public health epidemiologist be made available to perform this necessary function. And this is the idea which we must promote successfully if we are to see syphilis eradicated.

We now know beyond doubt that, insofar as treatment in public clinics is concerned, the medically indigent will probably never again constitute a critical proportion of patients with new syphilis. As long as we have penicillin, and as long as this drug remains effective, the bulk of syphilis will be treated privately.

Now let me summarize rapidly and then conclude. First, syphilis will have to be recognized generally by the medical profession as the serious and intolerable disease which it is, and every new case will have to be considered a cause for alarm.

Secondly, if syphilis is to be eradicated, the physician will have to make a decision, either to employ and train his own epidemiologic staff, at whatever cost and probable inefficiency, or to call on the public health epidemiologic assistant as he would call on the services of any other professional consultant. In either case, part of the job of treating the patient will be to prepare him to meet the syphilis epidemiologist as he would prepare him to meet any other specialist.

But to do this, he must have confidence in this third party and his method of operation. The possibility of violation of the privileged physician-patient relationship cannot excuse the neglect of epidemiology any more than it can excuse failure to refer any patient to any other specialist when the need for one is indicated. If, for any reason, the doctor or his professional associates feel that the professional relationship is in danger of jeopardy through existent public health practices with relation to syphilis, there is only one thing to be done. That is to get together with the public health authority and work out ways of operating so that it will not be in jeopardy.

But I seriously doubt that such a danger exists in most health jurisdictions in the country.

Syphilis is a Disease Which Should be Easy to Eradicate with the Tools We Have Today!

That syphilis is not only surviving but flourishing in its present proportions is a fact in which none of us can take pride, and in which we must all, as responsible citizens, be alarmed.

If we *want* to eradicate syphilis, we can do it, and with our present resources; but to do it, we will all have to work *together*—and I mean *really* together.

In closing, I would like to say that I for one would be willing to see the private physician diagnose and treat all the syphilis, and let public health attend exclusively to the epidemiology; to me this is the only solution which really makes sense.

Speaking frankly, as well as practically, I believe the effort to eradicate syphilis can be rewarding in many ways. The American public can be nothing but grateful to American medicine for having made that effort.

In dedicating himself to the eradication of syphilis, the private physician—both as a professional and as a citizen—has everything to gain and nothing to lose.

Communicable Disease Center
U. S. Public Health Service
Atlanta, Georgia 30333

What the American Medical Association Is Doing About Syphilis

CHARLES L. HUDSON, M.D.*

The American Medical Association has been alert to syphilis for a great number of years and, cognizant of its bearing on our national well-being, has waged continuous war on it. As early as the year 1874 the House of Delegates of the American Medical Association approved appointment of a committee to report on the most feasible plan for securing legislation to prevent the spread of syphilis. In June of 1876 President Marion J. Sims delivered an address on the status of the disease which the Association printed and distributed to put the public spotlight on syphilis. In 1899 it appointed a special committee to attend the International Conference for the Prevention of Syphilis, further recommending that a report be made on the best means of preventing the spread of syphilis.

The Association in 1903 made these resolutions: (1) To bring propaganda into the different states looking toward the proper recognition of dangers from venereal diseases; (2) to arrange for a national meeting to be held under the auspices of the Association for the prophylaxis of venereal diseases; and (3) to stimulate study and uniform knowledge on the subject of prophylaxis of venereal disease.

An important resolution adopted by the Association in 1917 stated that it commends the following as the basis for a program of civil activities:

1. That sexual continence is compatible with health and is the best prevention of venereal infections.

2. That steps be taken toward the prevention of venereal infections through prevention of prostitution, and by the provision of suitable recreational facilities, the control of alcoholic drinks, and other effective constructive measures.

3. That plans be adopted for centralized control of venereal infections through special divisions of the proper health and medical services.

Read at, Syphilis: A Symposium, Vanderbilt University School of Medicine, Nashville, Tennessee, May 17–18, 1963.

* Board of Trustees, American Medical Association; Associate Professor of Medicine, Cleveland Clinic Educational Foundation; Associate Clinical Professor of Medicine, Western Reserve University School of Medicine, Cleveland, Ohio

4. That the hospitals and dispensaries be encouraged to increase their facilities for early treatment and follow-up service for venereal diseases as a measure of national efficiency.

5. That the members of the medical profession be urged to make every effort to promote public opinion in support of measures instituted in accordance with these principles of action in the control of venereal diseases.

These were early efforts in combating the inroads being made by syphilis in American society.

In 1942, the Association called for the elimination of commercialized prostitution, and warned that a whole series of medical treatments given by physicians to prostitutes constituted unethical practice in the medical profession. And, most lately, it has cooperated with the American Social Health Association in the extensive mailing of a comprehensive questionnaire to private practitioners all over the country in an effort to determine by survey what the status of syphilis in our country is today. This knowledge is now available to the Public Health Service for evaluation and use in administering a new program directed at the eradication of syphilis.

In the area of medical education, the Association early recognized the need for more comprehensive study of the subject of syphilis and recommended, in 1921, "rapid extension of teaching facilities for the use of medical students whereby the knowledge of the medical, social and public health aspects of these diseases may be taught by actual clinical contact with patients under the direction of qualified teachers."

In this area, too, it asked its Section on Dermatology in 1921 to ascertain the actual history of syphilis, and to make this history available to students of medicine.

And in 1951, the Association, in its position as a watchdog of medical education in the United States, discovered "deficient teaching programs in dermatology and syphilology in some medical schools," and had its Council on Medical Education and Hospitals give proper attention to correct this flaw.

Additionally, a full-fledged educational program is continuously being carried on under American Medical Association auspices through numerous sessions at both Clinical and Annual meetings, devoted specifically to the subject of venereal diseases and syphilology. At the coming Annual meeting June 16 to 20, in Atlantic City, there will be a symposium on venereal diseases.

Articles such as the one which appeared in a recent issue of the Journal of the A.M.A., by Doctor R. H. Kampmeier, are constantly appearing in A.M.A. publications to keep the subject before the eyes of physicians everywhere.

At all opportunities, the Association's officials have urged local medical societies to take active cognizance of the war on syphilis and to lend support to the findings of the HEW Special Task Force on Syphilis.

The Special Task Force in reporting to the Surgeon General of the United States Public Health Service has urged the setting of a six-point,

ten-year goal for the elimination of syphilis as a public health hazard. The recommended points are:

1. An intensive national effort providing for at least two visits a year by a qualified health worker to the country's 100,000 general practitioners and one visit per year to the remaining 130,000 physicians.

2. Establishment of a program to insure that all blood processing laboratories report to health departments all positive specimens by name of patient.

3. Intensification and extension of current interview-investigation services to cover all infectious syphilis cases.

4. Development of a comprehensive and dynamic education program for professional workers and the general public.

5. Continuation of research in syphilis immunology, therapy and laboratory procedure and greater expansion of research in adolescent and young adult sex behavior.

6. Unstinted support of the program by Federal, State and local governments even after the reported number of syphilis cases begin to decline.

Reliable estimates indicate that infectious syphilis (reported and unreported) occurs in the United States at a rate of 60,000 cases a year, while the number of gonorrhea cases is estimated at one million. The total of 20,084 reported cases of infectious syphilis in 1962 was 7 per cent above the 1961 total.

People under 24 accounted for 45.7 per cent of reported syphilis cases and 55 per cent of reported gonorrhea cases. The 15–19 age group had the highest increase in incidence of infectious syphilis—10 per cent.

Nineteen states and 44 cities reported that more than 20 per cent of males named males as their sex partners.

Thirty-three states and 73 cities said prostitution was an increasing cause of venereal disease.

Concern must be felt in view of these alarming statistics. What is our present responsibility in this battle? We feel that private practitioners have the primary responsibility in our fight against syphilis. As Doctor Kampmeier states, they "still hold the key to eradication of syphilis because they treat more syphilitic patients in the office than are treated in public clinics." Case finding and the investigation of contact, methods long used by public health agencies, if adopted by the private practitioner might well prove to be the answer we are seeking.

Because Doctor Kampmeier, a physician well-published in this field, has had the foresight to wave a flag of warning in the face of many who have felt that syphilis, this bane of so many civilizations in history past, had been controlled, we tender him our collective gratitude, in the interest of national health, for his vigilance in this most important area.

Cleveland Clinic
2020 East 93rd Street
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Syphilis Through the Ages

WILLIAM L. FLEMING, M.D.*

This presentation will be focused on the origin of syphilis, on the development of our knowledge of this disease, and on what we know of factors affecting the incidence and prevalence of syphilis since the fifteenth century, in order to direct attention to the aspects of epidemiology most relevant to today's problems.

THE ORIGIN OF SYPHILIS

The controversy over whether syphilis existed in Europe prior to the return of the first expedition of Columbus from the Americas to Spain in 1493 will probably never be resolved. Consequently, it seems best to emphasize what seem to be the salient facts at the outset of this discussion.

There was unquestionably an epidemic of syphilis in a very severe form which swept over Europe and spread to other countries and continents in the latter part of the fifteenth and early part of the sixteenth centuries. Evidence of the pre-Columbian existence of syphilis in Europe has been very carefully examined mainly by the search of literature of various kinds for descriptions of the disease and by examining pre-Columbian bones for gross changes characteristic of syphilis. Suffice it to say that, while there is some disagreement as to the findings, the paucity of even alleged European pre-Columbian literary and osseous evidence of syphilis is striking. On the other hand, the abundant evidence that syphilis existed in the Americas at the time of Columbus' first voyage and the abundant evidence of the existence of pre-Columbian syphilitic bones in the Americas is equally striking. Consequently, the author is led to the conclusion that, while yaws and perhaps other spirochetal diseases even more closely related to syphilis undoubtedly existed in other parts of the world, the disease syphilis as we know it probably first appeared in Europe in the fifteenth century—possibly by spontaneous mutation of a spirochete already present

Read at, Syphilis: A Symposium, Vanderbilt University School of Medicine, Nashville, Tennessee, May 17–18, 1963

* Chairman, Department of Preventive Medicine, School of Medicine, University of North Carolina, Chapel Hill, N. C.

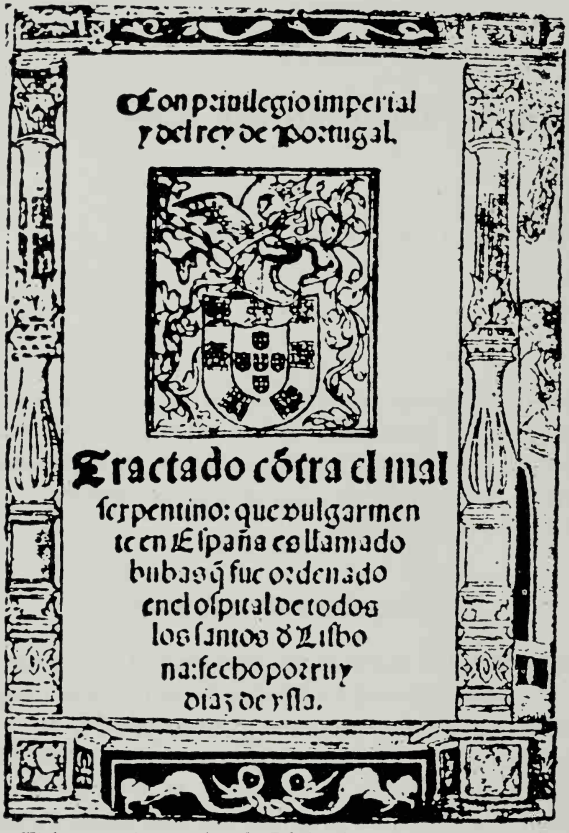

Con priuilegio imperial
y del rey de portugal.
Tractado cõtra el mal
serpentino: que vulgarmen
te en España es llamado
bubas q̃ fue ordenado
en el ospital de todos
los santos de Lisbo
na: fecho por ruy
dias de yssla.

Figure 1. Title page from Dias de Isla's *Treatise Against the Serpentine Disease.* (Jeanselme.)*

—but probably by introduction from without, and most likely from the Americas.

It has not been possible for the author (or for most of those writing on the subject) to examine original references and sources of evidence. Most of the historical information in this paper comes from Pusey,[1a] perhaps the most authoritative American historian of syphilis, who quotes not only early sources but such medical historians interested in this disease as Sudhoff, Block, Haustein, Williams and the latter's translation of Montejo. It has also been possible in the preparation of this paper to examine some of the writings of John Hunter,[2] Ricord[3] and Fournier,[4a] eminent clinicians of the eighteenth and nineteenth centuries, who added so much to our clinical knowledge of the disease, as well as publications of Buret,[5] a French nineteenth century historian of syphilis.

Pusey[1a] mentions the documentation given by some of the opponents of the American origin of syphilis professing to indicate that the great

* Figures 1 to 14 inclusive are from Pusey, W. A.: The History and Epidemiology of Syphilis. Springfield, Ill., C. C Thomas, 1933.

epidemic in Europe started a few years before the return of Columbus, but feels this evidence is unconvincing. Pusey feels that perhaps the best documentation of the beginning of the syphilis epidemic is provided by Montejo y Robledo, Spanish army surgeon, in a paper presented to the fourth Congreso Internacional de Americanistas at Madrid in 1882, which was publicized by Iwan Bloch in 1901. Williams, Rice and Renato-Lacayo[1a] examined Montejo's article and translated many of its passages. Montejo examined early Spanish chronicles of America. Oviedo[1a] in "Historia general y natural de las Indias" and Las Casas[1a] (whose father accompanied Columbus on the second voyage) provide particularly pertinent material as do other early historians[1a] of Spanish America—such as Pane, Saligua, and Hernandez—as to the existence of syphilis in the Americas and as to its appearance as a new disease in Spain after the return of Columbus. Perhaps the most convincing is Dias de Isla.[1a] Montejo examined his book "Treatise on the Serpentine Malady . . ." (Fig. 1), written between 1510 and 1520 and published in 1539, and even examined the original manuscript in the National Library of Madrid which contained some significant passages not in the published work. Dias de Isla was in practice in Barcelona in 1493 when Columbus' first expedition returned. Dias states very clearly that syphilis was unknown prior to 1493 and that it was introduced into Barcelona by the men of Columbus' vessels on their return from Española.

Figure 2. *The Impedimenta* (of the army). Triumph of the high and mighty Dame Syphilis, Queen of the Fountain of Love (*Le Triumphe de treshaulte et puissante Dame Verolle*). Lyons, 1539 (Anon.) (Jeanselme.)

Figure 3. *Syphilis*, 1496, Albert Dürer. (Bloch.)

Dias called syphilis the "Disease of the Isle of Española." Many of the crews of the vessels are said to have been infected, including one of the pilots. Dias treated several. Pusey quotes[1b] a passage from Dias as follows:

> It has pleased divine justice to give and send down upon us unknown afflictions, never seen nor recognized nor found in medical books, such as this serpentine disease . . . at the time that the Admiral don Xristoual Colon arrived in Spain, the Catholic sovereigns were in the city of Barcelona. And when they went to give them an account of their voyage and of what they had discovered immediately the city began to be infected and the aforesaid disease spread as was seen later on through long experience. . . . In the following year of 1494 the most Christian King Charles of France who was then reigning having gathered a great army passed into Italy. And at the time that he entered the country with his host many Spaniards

infected with this disease were in it and at once the camp began to be infected with the aforesaid malady and the French, as they did not know what it was, thought it came from the atmosphere of the region. The French called it the disease of Naples.

As Dias has outlined, King Charles VIII of France with an army composed of mercenaries—many from other countries—invaded Italy in the autumn of 1494 to seize the throne of Naples. There was little fighting, but Spanish soldiers sent to help protect Naples, together with other Spanish mercenaries in the French army, may have introduced syphilis. Armies of that day were accompanied by many female camp followers so the campaign, because of the absence of fighting, was more than usual a march of debauchery. A plague which most contemporary records attribute to syphilis attacked this army and by the spring of 1495 had forced its retreat from Italy. (Sudhoff[6a] almost alone among historians denies this epidemic was due to syphilis and attributes it to typhoid or paratyphoid.) An old woodcut of 1539 (Fig. 2) pictures the impedimenta of an army

Figure 4. Title page from Bartholomew Steber's *Syphilis*, 1497 or 1498. Probably the earliest illustration of syphilis. (Bloch.)

Figure 5. Title page from Grunpeck's *Tractatus de pestilentiale: Scorra sive mala d Franzos,* 1496(?). (Jeanselme.)

(possibly that of Charles VIII) as the "Triumph of the high and mighty Dame Syphilis, Queen of the Fountain of Love." Again, most contemporary records attribute the beginning of the epidemic in Europe to the dispersal of the mercenaries of Charles VIII's army over Europe.

Syphilis in local chronicles[1a] is said to have appeared in France Germany and Switzerland in 1495, in Holland and Greece in 1496, i England and Scotland in 1497, in Hungary and Russia in 1499. Agair while some have claimed references to syphilis in ancient Chinese literatur Pusey quotes[1a] Dohi of the University of Tokyo, whose studies indicate th spread of syphilis to Asia only after the epidemic in Europe and after visi of Portuguese explorers. Everywhere the disease was regarded as new an names for it appeared which attempted to shift the responsibility for it t others. "The Italians called it the Spanish or French disease; the Frenc called it the Italian or Neopolitan disease; the English called it the Frenc disease; the Russians called it the Polish disease; the Turks called it t

French disease . . . [and as previously mentioned] the first Spaniards who recognized the disease called it the disease of Española. . . ."[1c]

Publications regarding syphilis soon appeared in Europe. The first is accredited to Dürer in 1496 (Fig. 3). Steber[1a] in 1497 or 1498 is credited with the first illustration of a syphilitic, although Grunspeck's illustration[1a] may have appeared in 1496 (Figs. 4 and 5).

Another evidence cited in favor of syphilis' having been a new disease in Europe was its severity. For the first 50 years or so secondary syphilis tended to be accompanied by severe systemic symptoms which not too infrequently led to death.

In addition to the literature, the search for characteristic gross lesions of syphilis such as this skull[1a] (Fig. 6) from Peru by such authorities as Elliott Smith, Williams and Means has turned up many such pre-Columbian bones in both North and South America. There has been some dispute about a few European pre-Columbian bones, but their number is remarkably few and many authorities accept none as being both definitely pre-Columbian and syphilitic.

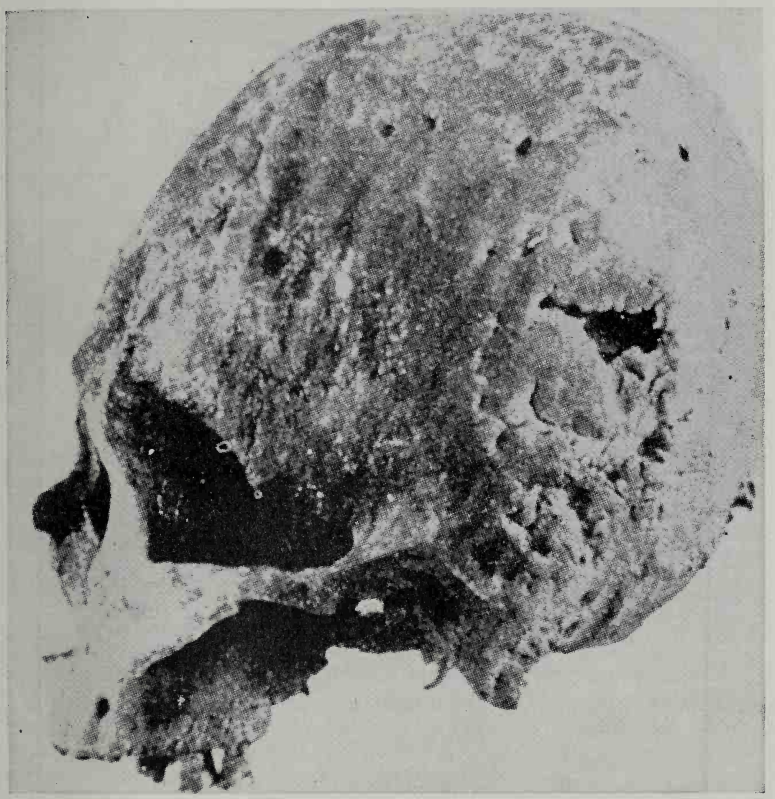
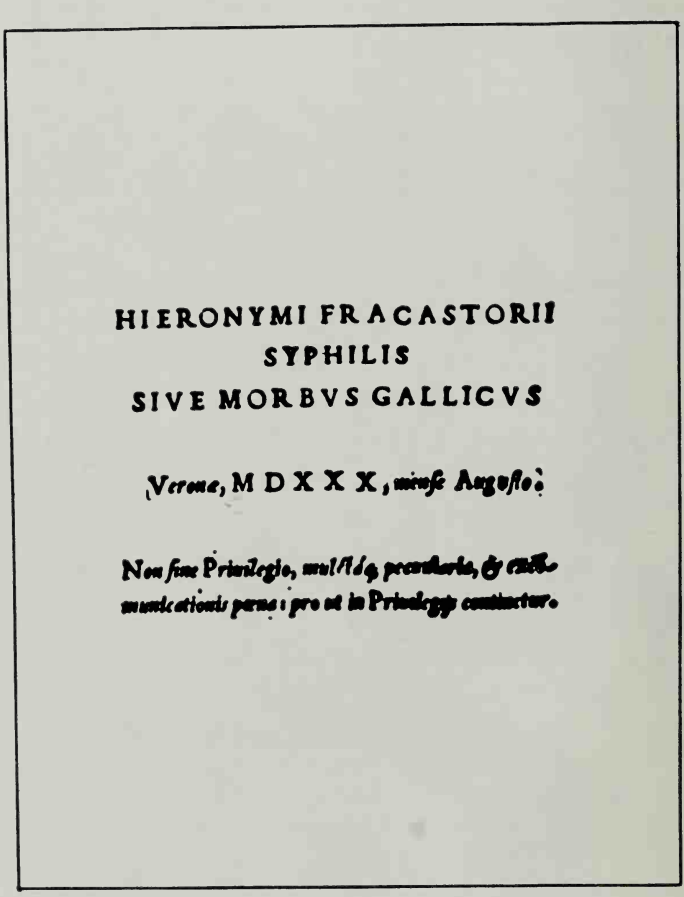


Figure 6. Ancient syphilitic skull from Paracas, Peru. (American Museum of Natural History—Williams.)

DEVELOPMENT OF KNOWLEDGE OF SYPHILIS

Understanding of the clinical characteristics of syphilis developed rapidly in the sixteenth century with the preoccupation of medical circles with the great epidemic as evidenced by the more than 40 authors of treatises on the subject. Fracastor, physician-author, who developed a theory of the microbic origin of infections, provided the name for the disease in his poem "Syphilis sive Morbus Gallicus" published in 1530 (Fig. 7). The importance of sexual intercourse in its transmission was recognized from the first, although poor hygiene made extragenital transmission relatively common. Congenital syphilis was soon recognized. Syphilis was fairly clearly differentiated from gonorrhea at first, but soon became confused with gonorrhea. The differential characteristics of the chancre were recognized and many secondary and late manifestations were described.[1-5]


HIERONYMI FRACASTORII
SYPHILIS
SIVE MORBVS GALLICVS

Veronæ, M D X X X, mense Augusto.

Figure 7. Title page from Fracastor's *Syphilis Sive Morbus Gallicus*. Actual size 5¾ x 8¼. (Crerar Library.)

Figure 8. The Pox. *Treatment of the venereal diseases by inunctions and inhalations.* Title page from Stephen Blankaart's *Venus belegerten Ontset,* Amsterdam, 1684. (Jeanselme.)

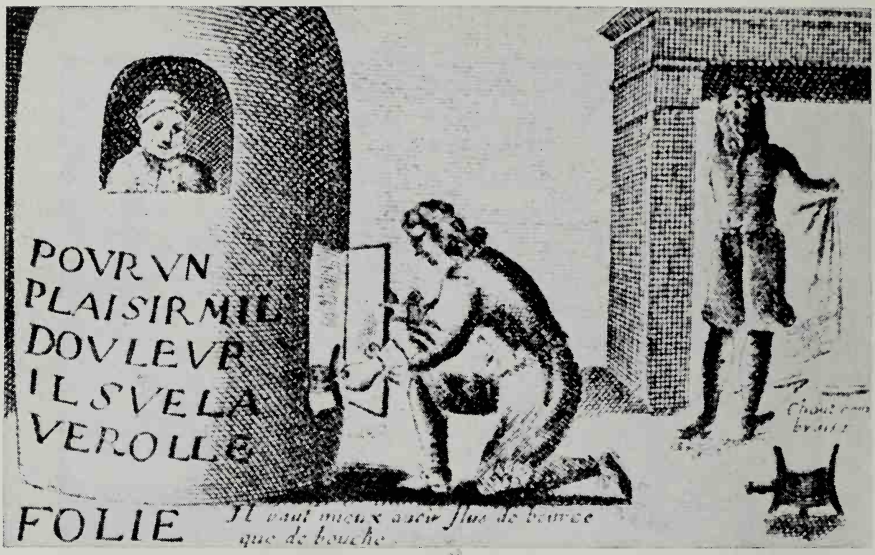


Figure 9. Fumigation (sweating treatment of syphilis). From the collection of engravings by Jacques Laniet of famous proverbs, Paris, 1659–1663. (Jeanselme.)

Not shown are interesting comments appearing at the bottom of the woodcut, which (translated) are as follows:

For one small pleasure I
suffer a thousand misfortunes.

I exchange one winter for two
miserable summers.

I sweat all over my body and
my jaw trembles.

I do not believe I will
ever see the end of my troubles.

Paracelsus is given credit for the introduction of mercury, but mercury was so commonly used in the treatment of skin disorders that it must have been tried empirically by many independently. Fever or sweating treatment was much in vogue as was treatment by mercury and other inunctions and inhalations, as is shown in these seventeenth century pictures (Figs. 8 and 9). Development of knowledge of syphilis continued rapidly during the seventeenth and eighteenth centuries but received a considerable set-back when John Hunter's self-inoculation experiment[2] led him to again consider syphilis and gonorrhea the same disease. The nineteenth century brought the great French syphilographers, perhaps chief among whom were Ricord and Fournier. Ricord again separated syphilis and gonorrhea. Ricord (Fig. 10), renowned for his wit, was firmly opposed to the theory of the American origin of syphilis, as is shown by his statement[5c] that the first sentence of the Bible really should be: "In the beginning, God created the heavens, the earth, man and venereal diseases," meaning that all venereal diseases had existed everywhere since the dawn of time. Ricord showed his close study of the disease by such aphorisms as "the bubo is not only the faithful companion of chancre but also a posthumous witness that long survives it,"[4b] and his impression of the seriousness of the disease by such statements as "the pox is a pitiless creditor and grants grace to no one."[4c] Olive

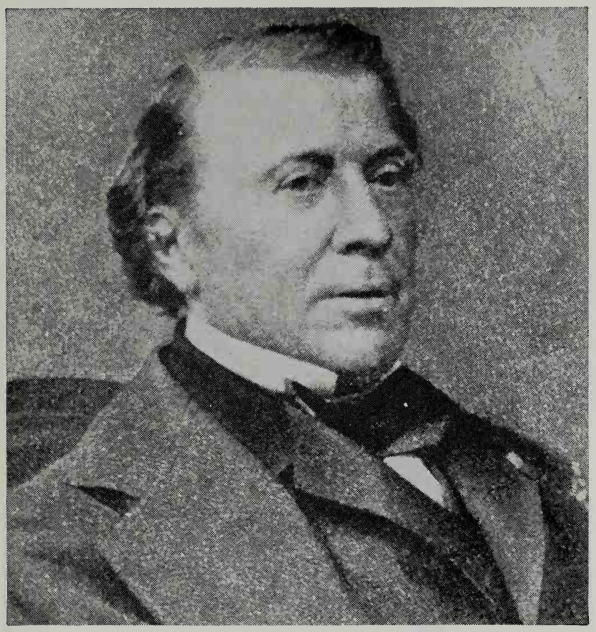


Figure 10. Phillippe Ricord (1799–1889).

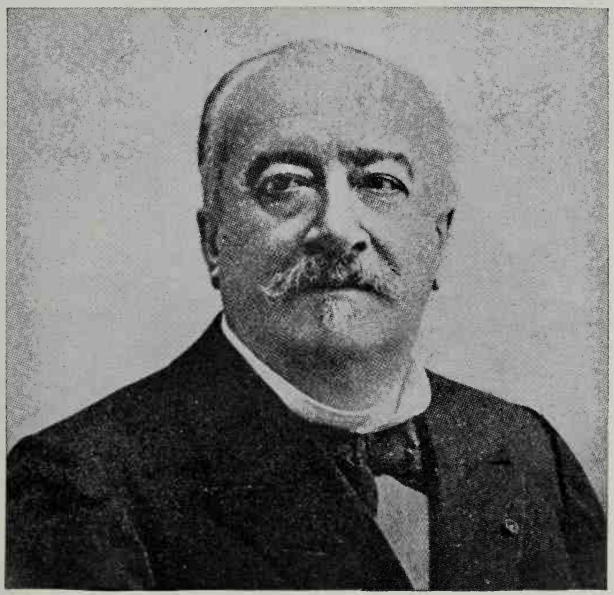


Figure 11. Jean-Alfred Fournier (1832–1914).

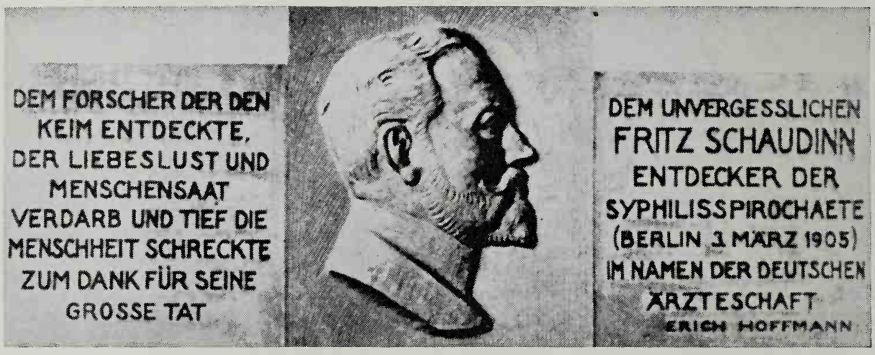


Figure 12. Tablet to Fritz Schaudinn (1871–1906).

Figure 13. Erich Hoffman (1868–1959).

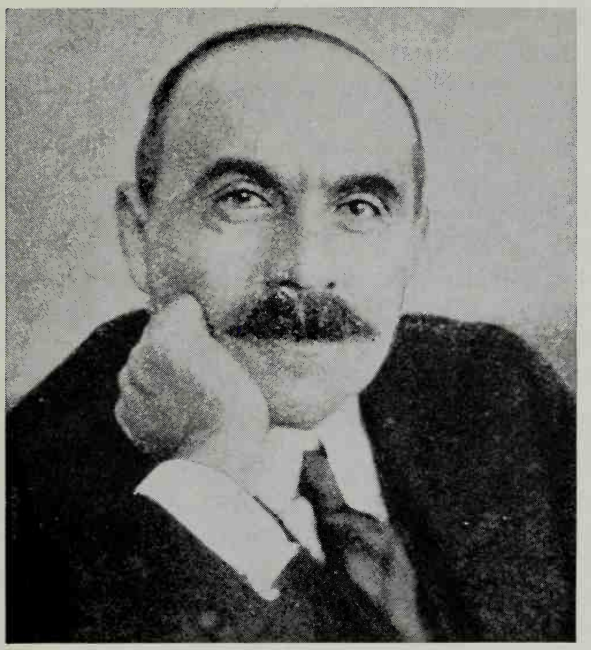


Figure 14. August von Wassermann (1866–1925).

Wendell Holmes called Ricord "the Voltaire of pelvic literature—a skeptic as to the morality of the race in general, who would have submitted Diana to treatment with his mineral specifics and ordered a course of blue pills for the vestal virgins."[6b] Fournier's (Fig. 11) knowledge of clinical syphilis (in spite of the absence of laboratory tests) was almost complete, including the relation of so-called parasyphilis, paresis and tabes. He systematized prolonged treatment with mercury and the iodides and in his remarkably perceptive book on "Syphilis and Marriage"[4a] showed that he possessed very good information on infectiousness in syphilis and did much to encourage physicians to help prevent the marriage of infectious or potentially infectious individuals since, as Dechambre quoted by Fournier[4d] said: "the pox, like the daily bread, is divided between husband and wife."

The early part of the twentieth century witnessed, as we know, in the short period of 1905–1910 the discovery of the causative agent by Schaudinn and Hoffman, the introduction of the complement fixation test by Wassermann, and the introduction of arsphenamine by Ehrlich in 1910 (Figs. 12, 13 and 14).

THE COURSE OF SYPHILIS IN THE WESTERN WORLD SINCE 1500

It is difficult for us today to come up with reliable information about the prevalence of chronic diseases, and we have even less information about

the past. "Syphilization" of Europe and the Western World proceeded rapidly after 1500. Prostitution would seem to have been a very important factor in its spread—and a much more important factor than today. Social factors operated as in the present age, and evidence from the literature, medical writings and history as to its relative frequency among upper social classes suggests much greater prevalence than today. Consequently, it is quite possible that syphilis had declined materially in frequency prior to the mid-nineteenth century. Nevertheless, we have chosen to focus on the prevalence of syphilis in the mid-nineteenth century, and on whether we have any evidence of a trend in the prevalence of syphilis between 1860 and 1910, a period of great social change but which preceded the advent of effective means of diagnosing and treating syphilis.

Syphilis: 1860–1910

There were serious attempts to estimate the prevalence of syphilis in the nineteenth century. Fournier and Erb[1a] are credited with estimating prevalence as 5 to 10 per cent based on use of history and clinical findings alone, and Neisser estimated the population of Berlin as being 12 per cent syphilitic, while Fournier estimated the population of Paris as being 15 per cent syphilitic.[7] Since they could diagnose latent syphilis only by history, it is difficult to believe that the availability of a serologic test would not have resulted in much higher estimates.

Haustein,[8] Hinrichsen,[9] and Siler[8] accumulated information on the incidence and prevalence of syphilis and other venereal diseases in military personnel since they constituted one of the few groups in the 1860–1910 period for which much information is available. Moore[8] examined these data to see if they could be used as indices of change in civilian populations of this period. These data are much more reliable in indicating changes within an army than in indicating differences between armies or in overall accuracy.

Moore[8] constructed figures which show some of these data. The first of these (Fig. 15) provides information on the Prussian Army, indicating a change in incidence of all syphilis from rates of 7.5 to 9.7 in the 1876–1886 period to 4 to 5.2 in 1910. In the British Army (Fig. 16) more accurate information as to the incidence of primary and secondary syphilis was available and indicates a change from rates of 101.8 in 1890 to 20.4 in 1910. Moore constructed a figure from Siler's data on the incidence of syphilis in the American Army (Fig. 17) which shows the upsurges connected with wars and the decline in the 1860–1910 period from rates of 70 to 25. In another figure (Fig. 18) Moore brought together data from the major armies of the Western World showing that with a few exceptions there were sizable decreases in reported military incidence and prevalence in the 1860–1910 period. World War I caused a considerable upsurge in syphilis as shown by data from the French and Dutch armies (Fig. 19).

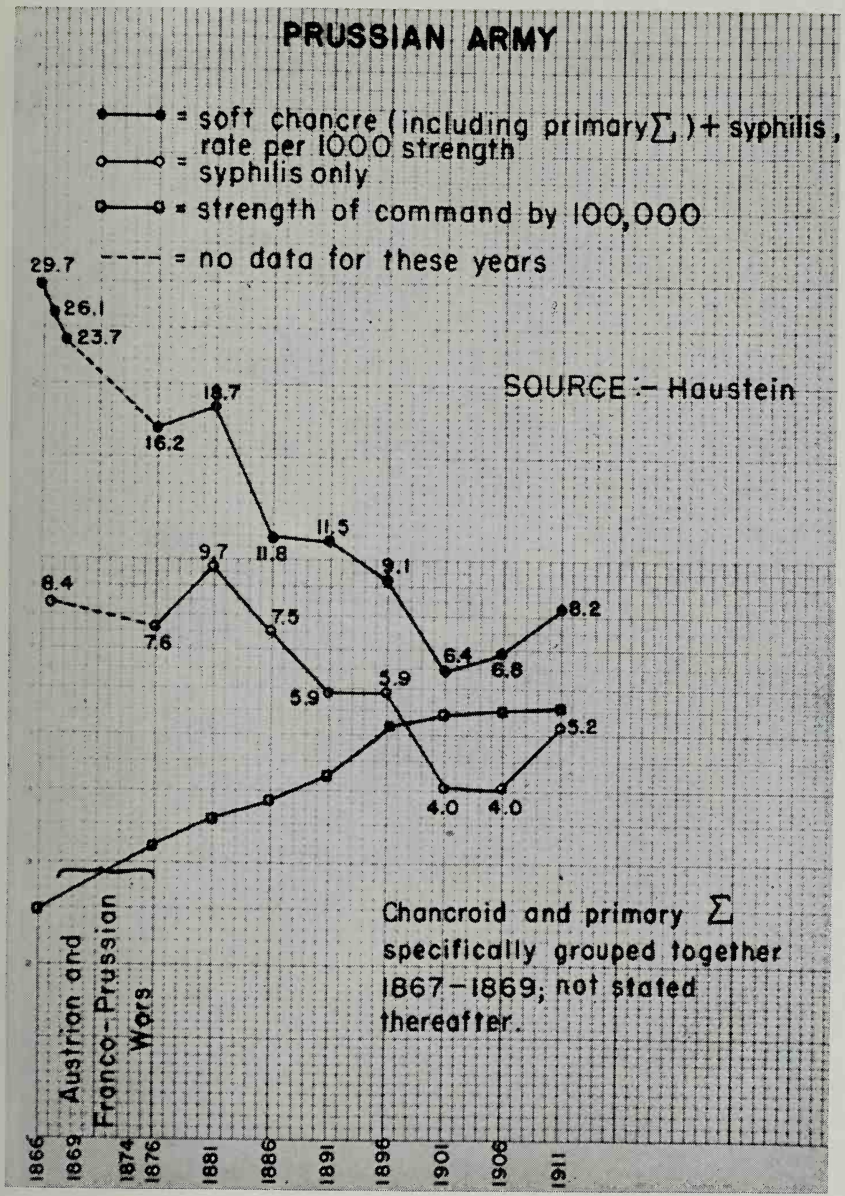


Figure 15*

* Figures 15 to 22 inclusive and Figure 25 are from Moore, J. E.: An evaluation of public health measures for the control of syphilis. Am. J. Syph., Gonor. & Ven. Dis. *35:* 101, 1951.

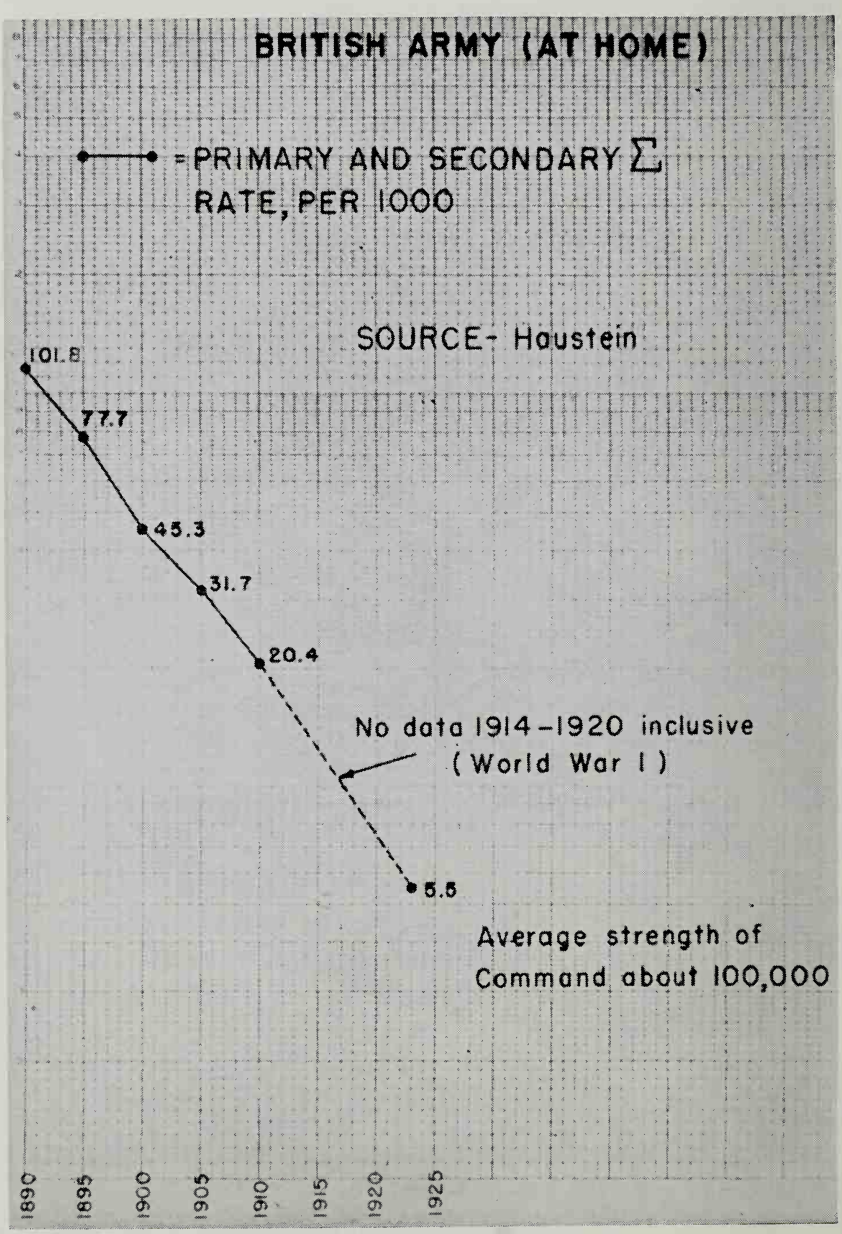

BRITISH ARMY (AT HOME)
= PRIMARY AND SECONDARY Σ RATE, PER 1000
SOURCE- Haustein
101.8
77.7
45.3
31.7
20.4
No data 1914-1920 inclusive (World War I)
5.5
Average strength of Command about 100,000
1890
1895
1900
1905
1910
1915
1920
1925

Figure 16

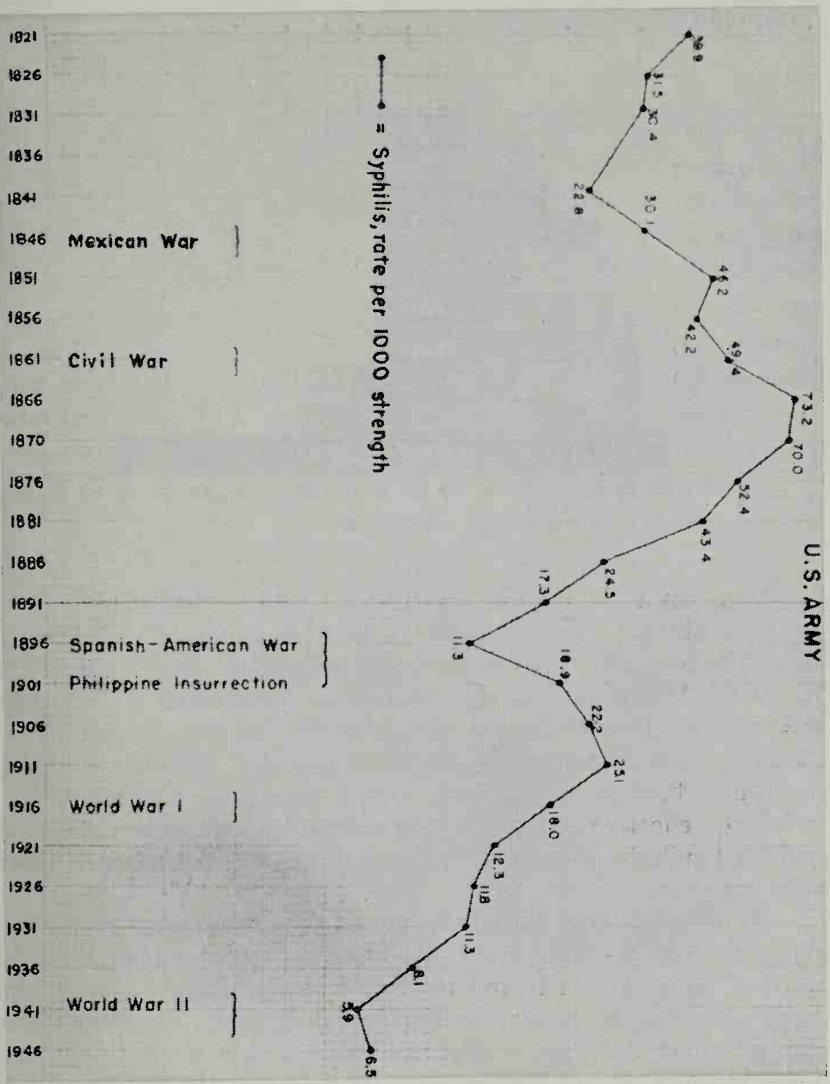


Figure 17. Syphilis in the U.S. Army.

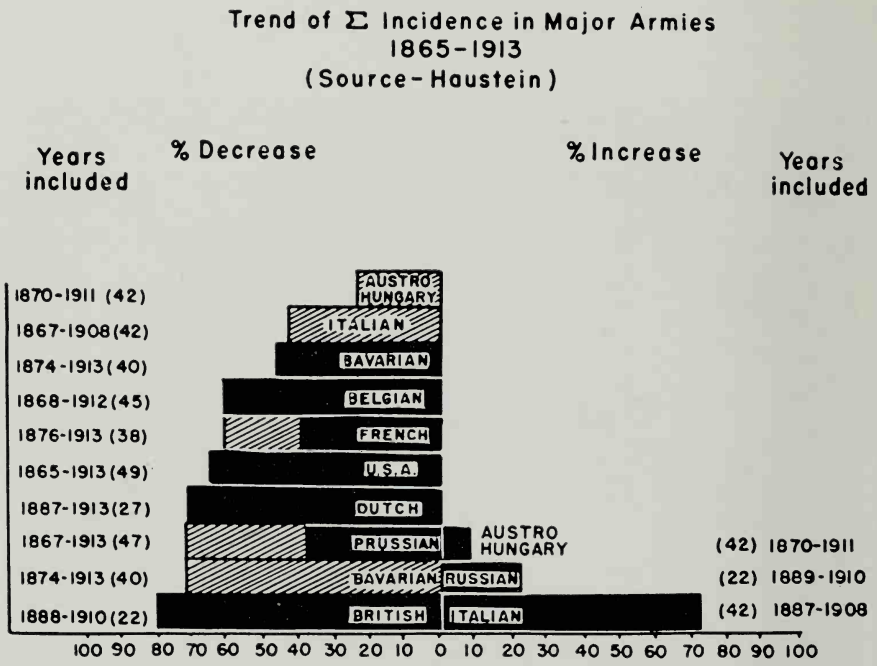


Figure 18

Crude as these indices are, they do suggest that there was a real decline in the incidence of syphilis in Western armies in 1860–1910, probably reflecting also declines in the civilian populations of the Western World. As Moore[8] pointed out, this decline can hardly be attributed in very significant measure to treatment or control measures. Mercury was the only treatment measure in use in this period which could have had any significant effect on infectiousness and there is little evidence that it was sufficiently effective and used widely enough to decrease the attack rate of syphilis. Similarly, there is no evidence that any specific control measures were important.

We do know that during this period there were great social changes going on in the Western World. The full effect of the industrial revolution was beginning to be felt and the standard of living was rising rapidly. Along with this rise in the standard of living, public education improved correspondingly. We know that there has always been a very uneven distribution of syphilis in the population, with syphilis being generally inversely proportional in prevalence to educational and economic status. Moore[8] reproduced a figure (Fig. 20) which shows the relationship of syphilis mortality to socio-economic status in England. Also, as part of the explanation, Moore reproduced a figure (Fig. 21) from Kinsey's data which shows evidence on the amount of extramarital intercourse as related to educational level and occupational class.

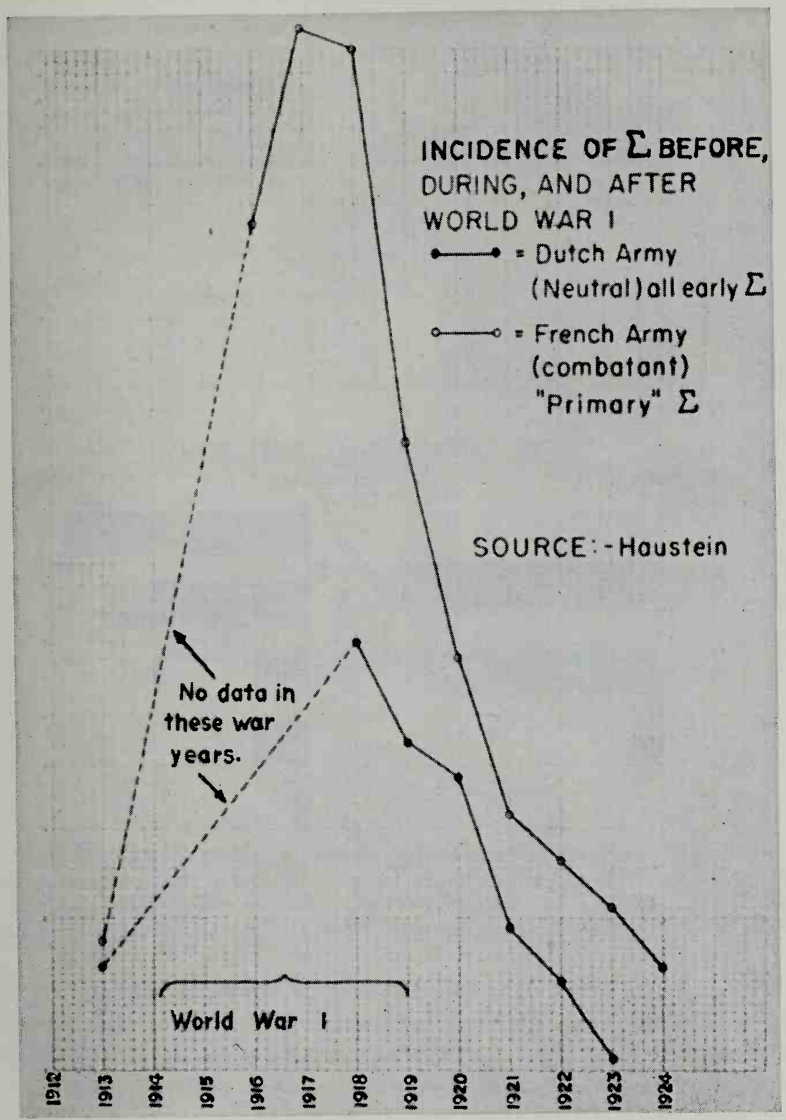

INCIDENCE OF Σ BEFORE,
DURING, AND AFTER
WORLD WAR I
= Dutch Army
(Neutral) all early Σ
= French Army
(combatant)
"Primary" Σ
SOURCE:-Haustein
No data in
these war
years.
World War I
1912
1913
1914
1915
1916
1917
1918
1919
1920
1921
1922
1923
1924

Figure 19

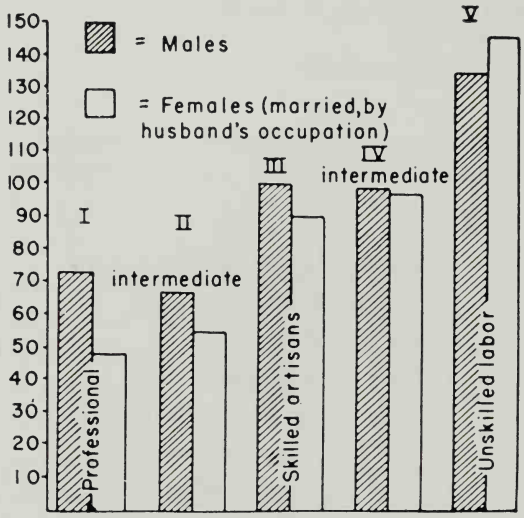


Figure 20. Ratio of actual to expected deaths (syphilis, tabes, paresis and aneurysm) by social class, ages 20–65 years, England and Wales, 1930–1932.

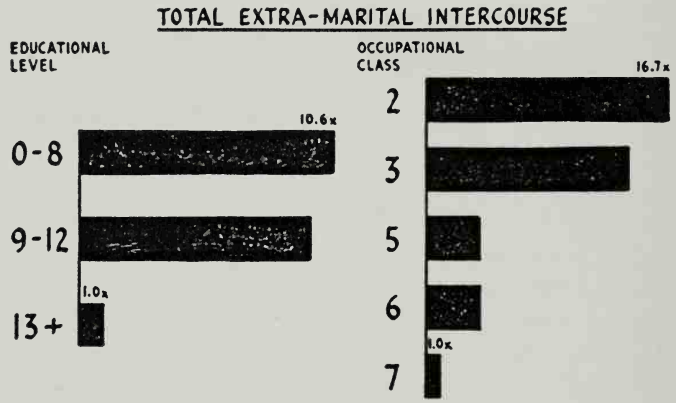


Figure 21. Extramarital intercourse, by educational level and occupational class. For single males of the age group 16–20. Relative lengths of bars compare mean frequencies for the groups. Note similarity of data based on educational levels and data based on occupational classes. (Kinsey et al.: Sexual Behavior in the Human Male.)

The purpose of reviewing this material for the 1860–1910 period, which suggests a real decline in syphilis due to social factors rather than treatment or control program, is to point up the fact that social factors have profoundly affected the prevalence of this disease before and *can do so again*. Also, we should keep in mind that social factors do not remain the same.

We should now examine what has happened to the incidence and prevalence of syphilis since 1910.

Syphilis: 1910–1938

This was the period after the introduction of effective arsenical treatment and of the serologic test and darkfield as tools in case finding. The

Scandinavian countries with effective public treatment and control programs reduced the attack rate of syphilis considerably (Fig. 22). In the United States the control program was weak except during World War I and probably did not have too much effect.

In 1938 Vonderlehr and Usilton[10] estimated that in the United States a person stood one chance in ten of acquiring syphilis before he died. The draftee survey of World War II furnished accurate information as to the prevalence of syphilis. Rates for positive serologic tests for syphilis in the draftee male age groups 18–40 (predominantly 21–35) were 1.8 per cent

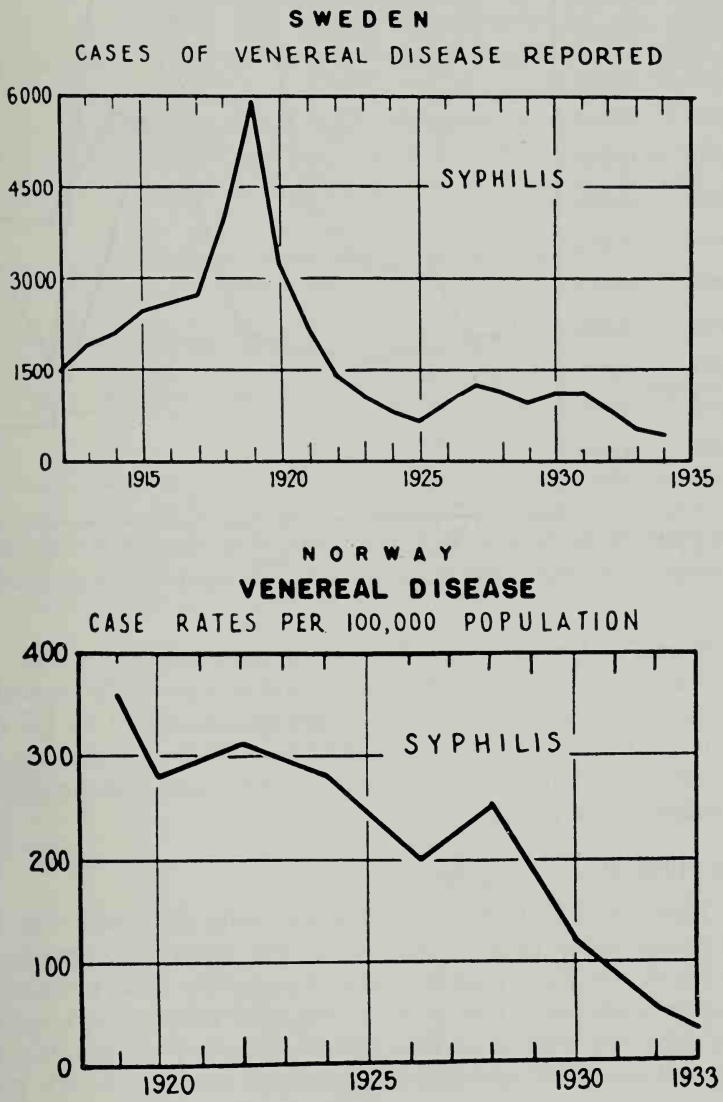


Figure 22

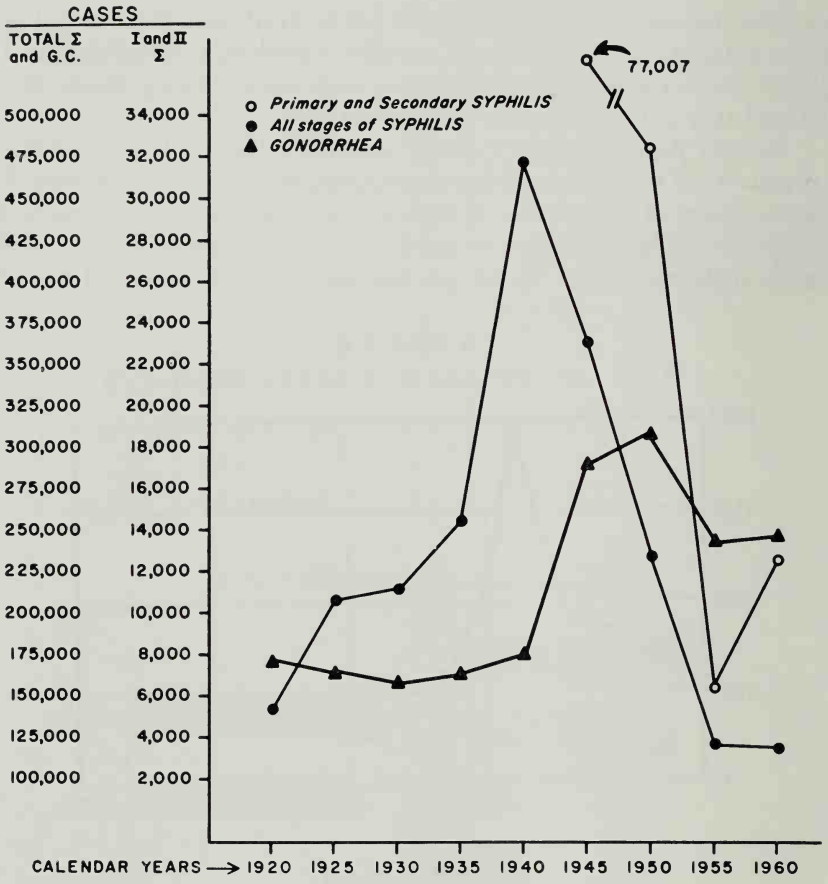


Figure 23. Reported cases of syphilis and gonorrhea in the United States.

for white and 24.5 per cent for Negroes, or an average of 4.6 per cent.[11] Extrapolating these figures for both sexes and all ages of the population of the United States, Parran and Vonderlehr[12] estimated that 2.4 per cent of individuals of the country, or one in 42, had syphilis at a given time. There were important sectional differences, with rates for both whites and Negroes being highest in the South.

Syphilis: 1938–1954

In 1938 the Syphilis Control Program really got under way in the United States under Parran's leadership. The upsurge of syphilis to be expected in World War II, on the basis of experience in all previous wars, was largely contained. The peak of reported primary and secondary syphilis cases was reached in 1947 and then a sharp decline in reported primary and secondary syphilis cases occurred, reaching the low point in 1954.

Syphilis: 1954–1958

During this period there was little overall change in reported primary and secondary syphilis cases.

Syphilis: 1959–Present

Following the low period of 1954–1958, reported primary and secondary cases rose sharply in 1959 and the upward trend has continued until the present. From the absolute low of 6251 cases of primary and secondary syphilis, or a rate of 4.1 in fiscal 1957, there has been a rise to 20,084 cases and a rate of 11 in fiscal 1962 (Figs. 23 and 24).

Factors in Post-War Fall. While few would doubt that the control program helped to bring the rate down after World War II, undoubtedly part of the decline would have occurred in any event following cessation of the war, as syphilis had declined following previous wars.

Possible Important Factors in Recent Increase. Penicillin was introduced in the treatment of syphilis in 1943 and its use became general

REPORTED SYPHILIS CASE RATE PER 100,000 POPULATION
FISCAL YEARS 1941 - 1961

Fiscal Year	Total Including Not Stated	Primary and Secondary	Primary, Secondary and Early Latent	Late and Late Latent	Congenital
		United States Civilians			
1941	368.2	51.7	134.4	153.9	13.4
1942	363.4	57.1	145.1	153.1	12.8
1943	447.0	63.8	179.8	195.7	12.6
1944	367.9	61.7	158.5	159.6	10.7
1945	282.3	60.5	140.5	111.8	9.7
1946	271.7	70.9	151.6	93.6	9.0
1947	264.6	75.6	152.0	86.5	8.7
1948	234.7	55.9	123.8	86.1	9.2
1949	197.3	37.1	94.7	83.3	9.8
1950	154.2	21.6	65.1	75.5	9.0
1951	131.8	12.1	46.8	71.1	8.5
1952	110.8	7.9	33.1	66.9	6.1
1953	100.8	6.2	27.0	64.7	5.2
1954	87.5	4.9	20.8	59.4	4.6
1955	76.0	4.1	17.5	52.7	3.4
1956	77.1	4.1	16.3	54.8	3.4
1957	78.3	3.8	15.2	58.1	3.3
1958	68.5	3.9	13.7	50.5	2.8
1959	69.3	4.7	14.9	50.1	3.0
1960	68.0	7.1	16.6	47.6	2.6
1961	69.7	10.4	21.1	45.0	2.4

Figure 24. (From VD Fact Sheets, 1961.[11])

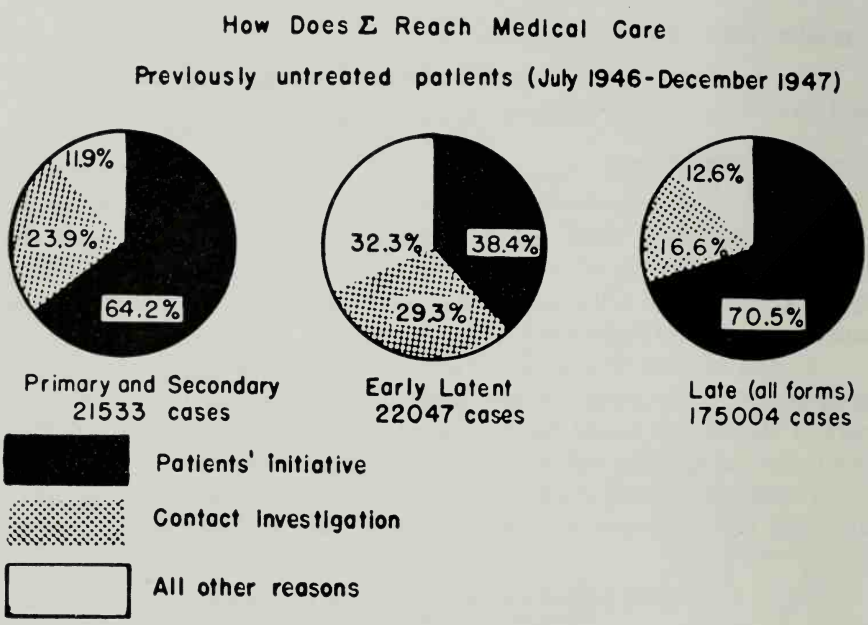


Figure 25

shortly after World War II. Since arsenic-bismuth treatment was unsuited but penicillin was suited to the doctor's office, the diagnosis and treatment of syphilis has shifted from the public clinic to the private doctor's office—and to an extent we have only recently learned. The National Study of Venereal Disease Incidence[13] has recently shown that only a little more than 10 per cent of cases of infectious syphilis treated by private physicians are being reported, and that while only 20,000 cases of infectious syphilis were reported by clinics and physicians, probably closer to 100,000 were diagnosed and treated in fiscal 1962.

The potential loss to the control program arising from the omission of contact investigation of infectious syphilis cases—which is more difficult for cases handled by private physicians than those in public clinics—is shown by Figure 25 from an article by Moore.[8]

NEXT STEPS

It is completely clear today, as some have been saying for years, that the private physician will have to be brought into the control program before syphilis can be controlled. Studies have shown that private physicians can be educated to report cases of syphilis and to cooperate with having contact investigation carried out on their cases of infectious syphilis.

This teaming up of the private physician and the health department in the field of venereal disease control may lead the way to closer cooperation in other fields and this partnership might become as important as venereal disease control itself.

Also, the fact that social forces decreased the attack rate of syphilis before effective treatment and control efforts became possible should make us realize that social factors can change and that possibly some of the recent increase may be due to social factors. We know that change in treatment methods and the economic status of the population has made the private physician more important than the clinic and we also know that even factors in the epidemiology of syphilis may change. Recent evidence points to the greater importance of homosexual practices in the spread of syphilis today. Also, syphilis has always been acquired mostly by the young, and perhaps the teen-ager may be becoming an even more important factor. Intensive research of this disease and the conditions under which it is transmitted obviously must continue, and even be intensified in order to insure our ability to control it.

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The Oslo Study of the Natural Course of Untreated Syphilis

An Epidemiologic Investigation Based on a Re-study of the Boeck-Bruusgaard Material

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NIELS DANBOLT, M.D.**

Nowhere in the world was there a more unique opportunity to learn what happens when early syphilis goes untreated than from the files of Professor Boeck of Oslo, Norway. His deep scientific conviction as to the inadequacies of the specific treatment of his time led him to withhold treatment from 1978 patients with primary and secondary syphilis during the 20-year period 1891–1910. Community protection from infection was aided by the hospitalization of these patients until all traces of the disease had disappeared (from 1 to 12 months, average 3.6 months). In 1929, his successor, E. Bruusgaard,[1] reported on a follow-up study of 473 of these patients and provided information on the outcome of untreated syphilis, which formed the basis for prognostic statements on syphilis for more than 25 years. From 1948 to 1951, in the department of Bruusgaard's successor, Professor Niels Danbolt, Trygve Gjestland carefully planned and executed an epidemiologic re-study of this unique clinical material in its entirety.[2] The study method and the results should be of interest to all physicians and public health workers.

The objectives of this paper are: (*a*) to review and appraise this important contribution to the syphilologic literature; (*b*) to present some of the details of the planning and execution of the investigation; (*c*) to provide a brief resume of the results of the study for the American literature and (*d*) to emphasize the significance of this investigation for the natural course of chronic disease.

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The initial phase of this study began in 1948 with the original suggestions of Drs. J. E. Moore, N. Danbolt, T. Guthe and others. These suggestions were incorporated by Gjestland into a plan which included: (1) definition of the nature, extent and significance of this problem, a clarification of the objectives and a proposal of important questions which might be answered by a re-study of this material; (2) appraisal of existing information; (3) formulation of hypotheses; (4) testing of hypotheses and (5) conclusions and practical application.

The nature of the overall problem was quoted from Stokes:[3] "No one who has had even a limited experience in answering the questions on which students and physicians seek information in their practical contacts with the disease can fail to realize that the great ailment of modern syphilological practice is a lack of comprehension of the why and wherefore, rather than the what to do." Comprehension of the "why and wherefore" lay in a better understanding of the prognosis of untreated syphilis. The beneficial effects of treatment in modifying the biologic course of syphilitic infection is well known. What was lacking was quantitative information on what happens to those who go untreated. The reason for this lack lay in the absence of studies of large groups of untreated patients, thoroughly diagnosed and observed over sufficient periods of time.

Further significance of the problem of prognosis is emphasized by the reliance of modern syphilologists upon the results of Bruusgaard's investigation of only 473 of Boeck's 1978 patients in 1925–1927.

Of prime importance in determining the potential contribution of this investigation were the examination of the diagnostic criteria of those times and an analysis of the validity of the diagnoses made in Boeck's department. These diagnoses were based entirely on clinical examination and subsequent observation (because neither darkfield nor serologic tests for syphilis were employed before 1910). A large sample of the hospital records were examined carefully by the authors of this review and in their opinions there is no doubt that a great majority of these patients had early syphilis.

The objectives of the Oslo study were stated as follows: "(1) To trace as many patients as possible to an 'end point,' defined as the last observation, living or dead; (2) to collect the maximum amount of clinical data (including data on treatment) on each patient from the date of his original discharge from Boeck's department through the interim period and up to the 'end point'; (3) to determine the causes of death through a study of post-mortem examinations, hospitalizations, death certificates, etc., with the maximum amount of accuracy, and (4) to examine at the Rikshospitalet as many living patients as possible and to employ as complete examinations for syphilis as circumstances will permit and to have examined elsewhere according to the same principles those patients who, for some reason or other, could not be brought to the Rikshospitalet."[2]

The questions asked from the beginning were: What is the final out-

come in terms of late syphilis, duration of life and causes of death in persons who are untreated for symptomatic early syphilis?

The appraisals of existing information were limited to: (*a*) classification and critical evaluation of other investigations on the outcome of untreated syphilis and (*b*) well known authoritative reports dealing with the various aspects of syphilitic infection: secondary relapse, benign late syphilis, cardiovascular syphilis, neurosyphilis, etc. Gjestland's evaluations of the literature on these specific aspects of syphilitic infection in relation to his own data are among the worthwhile contributions of this investigation, particularly the presentation and evaluation of the essential items to consider when comparisons between studies are attempted.

Following an appraisal of the most pertinent literature, a careful study of the Boeck records and a detailed and critical appraisal of Bruusgaard's results, the next step was to consider the specific questions for which the Boeck data might provide answers. Thus, among patients untreated for primary and secondary syphilis and with no, some, or unknown subsequent treatment: (1) What are the frequencies of secondary relapse, of benign late syphilis, of late symptomatic syphilis, of life-long latency and of spontaneous cure? (2) What are the effects on longevity, on causes of death and on mortality over that of nonsyphilitics? (3) Does age at time of infection influence outcome? (4) Does sex influence outcome? (5) Is morbidity from conditions other than syphilis greater than among nonsyphilitics?

On the basis of these questions and on the appraisal of pertinent literature, the study was designed to provide support or denial of the following hypotheses: (1) Syphilis, untreated in its primary and secondary stages, has a favorable outcome in a majority of instances. (2) Serious results are more frequent in males than in females. (3) Untreated syphilis prolongs the period of community danger of infection. (4) There is no way to predict the outcome in individual cases. (5) Syphilitics have a higher morbidity and mortality from other conditions than do nonsyphilitics.

DESIGN OF INVESTIGATION

The study group finally decided upon comprised 1404 individuals drawn from Boeck's original series of 1978 hospitalized patients. The ones eliminated were 574 Norwegian nonresidents of Oslo and non-Norwegians. It was believed that limiting the tracing to Norwegian residents of Oslo would not bias the overall study and at the same time would simplify tracing and aid in the selection of controls.

The 1404 Norwegian residents of Oslo came from the underprivileged section of society which at that time lived in the east zone of the city. There were 958 females and 446 males. Between the ages of *0–14*, there were 41 females (4.2 per cent) and 32 males (7.2 per cent); ages of *15–24*,

591 females (61.7 per cent) and 208 males (46.7 per cent); ages of *25–39*, 268 females (28.0 per cent) and 171 males (38.3 per cent) and in the *40 and over* group, 58 females (6.1 per cent) and 35 males (7.8 per cent).

Among both males and females the highest proportions were among the 15–24 age groups and the next highest among those 25–39 years of age.

The "Search Order"

The complete plan of investigation cannot be given in detail here, but the thoroughness with which this plan was considered and undertaken and the method of search and identification is an outstanding example of careful planning. Two essential preliminary requirements for retrospective studies of this kind are the establishment of a "search order" and a system of identification of names and recorded data. A "search order" is a listing of possible sources of information in pre-arranged order which will assure a minimum of duplication of effort and, if followed routinely, will add a considerable degree of accuracy to the identifying process. Every name should be seached through the entire list even when it appears to have been located in the first source searched. Similarities of name and other identifying data make this necessary. Identity can be established objectively only by comparing a number of personal, geographic and clinical characteristics each time new information is found.

Chief Sources of Information and Order of Search. The following is a list of the sources of identifying and clinical information, arranged in the order in which they were searched. This is the "Search Order" through which each name was taken.

1. Death registers
2. The Department of Dermatology and Venerology of the Rikshospitalet
3. The Oslo Bureau of Indigents
4. Bureaus of Indigents elsewhere*
5. The Central Bureau of Statistics' Marriage Registry for Oslo (women only)
6. The Oslo Population Register
7. The Oslo City Health Department, Venereal Disease Division
8. The Municipal Hospital of Oslo, Venereal Disease Division
9. Parish minister, sheriff or local Population Register at patient's place of birth*
10. Parish minister, sheriff or local Population Register at patient's place of residence prior to his settling in the City of Oslo*
11. Individual sources, especially relatives of the patient, but also many others not specified*
12. The Oslo City Health Department and the Central Bureau of Statistics (for transcription of death certificates)
13. Mental hospitals, psychiatric wards, neurological and other hospital wards (private practitioners as indicated)

Collection of Data

From time to time the operation required and received the cooperation of various hospital staffs and many persons employed in the official record bureaus of the country. Every bit of information found on every patient was checked according to the identification plan and all records (hospital

* These are supplemental sources.

and others) were recorded *in toto* in the master record folder. The record system, organized before the tracing began, comprised: (*a*) an index card file which served as a key to the other files and an index of the current status of tracing on each patient; (*b*) a master folder which contained the transcribed records from hospitals, admitting agencies and physicians' offices and (*c*) a summary record devised to permit analysis of the material as efficiently as possible in terms of the proposed questions and to give information on the natural course of syphilis infection.

At the close of the investigation in August, 1951, some usable information had been obtained on 81.7 per cent of the 1,404 study group. In Table 1 are the results of the tracing efforts. The "known" group comprises those on whom a diagnosis could be established at a classifiable "end point." They were alive and examined during the investigation period, or if dead, the time and status at death could be determined. "Partially known" refers to those with one or more observations during the years following discharge from Boeck's department, but not to the same clear-cut "end points" of diagnosis as those of the "knowns." "Unknown" means no information following discharge from Boeck's department. For 83.9 per cent of the males and for 80.7 per cent of the females there was some significant information. Still alive in 1951 were 16.1 per cent of males and 19.5 of females. This is a high and probably unique degree of success in tracing a population group some 40 to 60 years after the original event.

On the 953 persons classed as "known" there were 3584 recorded observations (an average of 3.8 per person), and on the 194 "partially known," 523 observations (2.7 per person), the overall average being 3.6 observations. Of the "knowns," 259 were still alive (Table 1) and of these, 83.4 per cent were examined in Norway or elsewhere during or shortly prior to the period of investigation (1949–1951). For the remaining 16.4 per cent (43 persons), information was obtained directly or indirectly as to their health status. Information on the dead (694 persons) came from physical examinations immediately prior to death in approximately 29 per

Table 1. *Oslo Study of Untreated Syphilis: Tracing Status ("Known," "Partially Known," and "Unknown") 1951, by Sex*

TRACING STATUS	MALE		FEMALE		TOTAL	
	No.	Per cent	No.	Per cent	No.	Per cent
"Known"						
Living	72	16.1	187	19.5	259	18.4
Dead	259	58.1	435	45.4	694	49.4
Subtotal	331	74.2	622	64.9	953	67.9
"Partially known"	43	9.6	151	15.8	194	13.8
Subtotal	374	83.9	773	80.7	1147	81.7
"Unknown"	72	16.1	185	19.3	257	18.3
TOTAL	446	100.0	958	100.0	1404	100.0

cent, from autopsy examinations in 30 per cent, from physical examinations a short time prior to death in 15 per cent and from death certificates or other sources in 26 per cent.

RESULTS

For conclusions and practical applications, the collected and analyzed data are presented to show the extent to which the questions have been answered and the hypotheses verified for practical use. The results are given and discussed under the following chapter headings in Gjestland's monograph:[2] Clinical Secondary Relapse; "Benign" Late Syphilis; Cardiovascular Syphilis; Neurosyphilis; Other Late Syphilis; Mortality; and Spontaneous Cure. Only brief and incomplete presentations of these results can be made in this paper.

Type of Lesion

Clinical Secondary Relapse. This is one of the most significant of the analytical sections, contributing much to knowledge of the natural course of syphilis; so much, in fact, that the entire concept of relapse may be modified as a result of these findings. Although the opinion is not universal, much of the modern literature states that clinical secondary relapse is a phenomenon related only to inadequate treatment of early syphilis or must be regarded as progression. The Oslo study shows conclusively that clinical secondary relapse occurs in the absence of treatment.

Among the 244 patients (23.6 per cent) who developed relapse, 46 (18.9 per cent) experienced two; 8 (3.3 per cent), three and 1 (0.4 per cent), four outbreaks; i.e., multiple outbreaks occurred in 22.5 per cent. Furthermore, both from the clinical and public health standpoints it is important to note that in 85 per cent of instances the relapsing lesions involved the mouth, throat or anogenital regions.

More than two-thirds of the relapsers had relapsed by the end of six months (males 72.3 per cent, females 65.1 per cent); by the end of a year, 92.3 per cent and 86.6 per cent; at two years, 96.9 per cent and 93.3 per cent and by the end of five years, 100 per cent.

Benign late syphilis occurred in 14.4 per cent of males and 16.7 per cent of females. This is in general thought to be related to an upset in the parasite-host relationship resulting from reactivation of remaining treponemes in a sensitized host.

In males this was higher in the 0–14 and 40 and over infected age groups and in females higher in the 15–39 age group. Of those observed with benign late syphilis, 25 per cent of the males and 34.7 per cent of the females had from two to seven episodes of this manifestation, showing again a rhythmic feature of this disease. Solitary (single structure) lesions were more common (90 per cent) than multiple structure involvement;

70 per cent were skin, 9.6 per cent skeletal and 10.3 per cent mucous membrane lesions. In the remaining 10 per cent, which were multiple structure lesions, the skin was one of the structures involved in more than half of the instances. Lesions developed from the first to the forty-sixth year after the healing of secondaries, the majority developing by the end of the fifteenth year. When the probabilities were calculated, males and females showed significant differences at 15, 30 and 35 years, females being higher in each instance.

Cardiovascular Syphilis. Of particular interest is the fact that *none* of those infected before the age of 15 were found to have this type of late syphilis and, as expected in each age group, the proportions of males were significantly higher than those of females, the total rates for males being almost twice that for females, 13.6 per cent and 7.6 per cent, respectively.

Neurosyphilis. Of the 62 persons in the group under study who developed neurosyphilis, 31 (9.4 per cent) were males and 31 (5.0 per cent) females. The lesions were divided as follows: diffuse meningovascular syphilis (males 3.6 per cent; females 1.7 per cent); general paresis (males 3.0 per cent; females 1.7 per cent); tabes dorsalis (males 2.5 per cent; females 1.4 per cent) and gumma of the brain (males 0.3 per cent; females 0.2 per cent). It is of interest here to note that neurosyphilis *did* develop among those infected under the age of 15. Of this age group, 6.1 per cent developed neurosyphilis, with a male-female ratio of approximately 4 to 1. None of the 28 males over 40 at infection developed neurosyphilis, whereas two of 45 females did.

Of the 62 persons with neurosyphilis, 18 were alive and examined during the period of the investigation, these being equally divided among males and females. Of the dead, neurosyphilis was recorded as the primary cause of death in two-thirds of the instances. In the other third, neurosyphilis was present but unrelated to the cause of death.

Other Late Syphilis. Among 953 patients classified as "known," only two were found to have other types of late syphilis. Two females had gummas of the liver, one found at autopsy and one diagnosed clinically. In each instance the manifestation was considered to be the primary cause of death.

Mortality

The mortality of this series of patients was studied by Gjestland from three viewpoints: (*a*) the actual causes of death; (*b*) the probabilities of dying primarily as a result of syphilis infection, and (*c*) the excess mortality of syphilitics as compared with a control series.

Table 2 shows the primary causes of death among the 694 known dead. Syphilis was the primary cause of death in 15.1 per cent of the males and 8.3 per cent of the females, a ratio of 1.8 to 1. Among males, syphilis ranked second and among females, fifth as a cause of death. In each group, tuberculosis led the causes of death and in females more died of cancer

Table 2. *The Oslo Study of Untreated Syphilis: Primary Causes of Death by Sex Among 694 Known Dead*

PRIMARY CAUSES OF DEATH	MALES			FEMALES		
	No.	Per cent	Rank	No.	Per cent	Rank
Tuberculosis	45	17.4	1st	74	17.0	1st
Syphilis	39	15.1	2nd	36	8.3	5th
Cancer and other tumors	32	12.4	3rd	71	16.3	3rd
Diseases of circulatory system	28	10.8	4th	72	16.6	2nd
Diseases of respiratory system	25	9.7	5th	42	9.7	4th
Sudden—unknown, unspecified	20	7.7	6th	18	4.1	8th
Diseases of urinary and genital tract	16	6.2	7th	16	3.7	9th
Diseases of nervous system and sense organs	14	5.4	8th	34	7.8	6th
Accidental deaths	11	4.2	9th	9	2.1	10th
Diseases of digestive system	7	2.7	10th	24	5.5	7th
All others	22	8.7		39	8.9	

and diseases of the circulatory and respiratory system than of syphilis. Thus, among a 100 per cent syphilitic population, 84.9 per cent of males and 91.7 per cent of females died of other causes.

The cumulative probability of dying directly as a result of syphilis was 17.1 per hundred in males and eight per hundred in females by the end of 40 years of infection among this group of patients.

In order to study possible cause-and-effect relationships for the excess mortality of syphilitics over nonsyphilitics, a control group was chosen from the population of the City of Oslo for comparison with the mortality experience of Boeck's patients. It was found that most of his patients came from the eastern parishes of the city and their mortality experience could be compared by age, sex and cause and by decade with the population from which they came. This was studied in considerable detail and will be reported in detail in a separate publication.[4] Certain of these findings are touched upon in Table 3 and the following paragraph.

Table 3 shows that these untreated syphilitics had an excess in mortality over that expected of 53 per cent in males and 63 per cent in females (all ages), and there was some degree of excess in every age group except males 10–19. The excess was most pronounced in males 40–49 and in females 30–39. A similar picture of excess mortality was found when the mortality experiences of the eastern and western parishes were compared according to age, sex and decade; the eastern group with lower economic status showed excess mortality over that of the west in practically every category of comparison. The average excess mortality of the east over the west (all ages) was 16 to 27 per cent among males and 25 to 38 per cent among females.

Table 3. *The Oslo Study of Untreated Syphilis: Mortality Excess in Syphilitics as Compared to That Expected on Basis of Experience of Residents of Eastern Parishes of Oslo by Age and Sex from 1890–1940*

AGE	MALES			FEMALES		
	Expected	Observed	Excess Per cent	Expected	Observed	Excess Per cent
10–19	2.3	1	0	4.4	5	14
20–29	13.7	15	0	29.4	42	43
30–39	21.5	33	53	43.1	84	95
40–49	24.8	55	122	36.8	69	88
50–59	30.5	48	57	38.3	60	57
60–69	28.4	41	44	26.6	41	54
70 and over	18.9	21	11	25.3	31	23
All ages	140.1	214	53	203.9	332	63

Spontaneous Cure

There are many statements in the literature about the frequency of spontaneous cure, but very little evidence is available to support the estimates. One of the barriers to an understanding of this problem is the strictness of definitions of spontaneous cure made by various authors. These definitions of spontaneous cure are too rigid to permit quantitative evaluation. More practical is a consideration of the extent of disability during the lifetime of the persons involved. It was estimated that between 60 and 70 out of every 100 of these patients went through life with a minumum of inconvenience despite no treatment for early syphilis. This gives no encouragement to withhold treatment because the final outcome in any individual cannot be predicted and, too, syphilis is still a transmissible disease when untreated and can cause serious difficulties among 30 to 40 out of each 100 who remain untreated.

SUMMARY

This re-study represents a striking example of the application of the modern epidemiologic approach. In addition to the scientific contribution of this investigation, an outstanding illustration of international scientific cooperation has been demonstrated.

The remarkable degree of success in obtaining significant information on approximately 80 per cent of the study group, 1404 Norwegian residents of Oslo of 1891–1910, was undoubtedly due to the careful planning which preceded the tracing efforts. This planning included: (*a*) a consideration of the nature, extent and significance of the problems of untreated syphilis;

(*b*) an appraisal of existing information on the subject; (*c*) the setting up of hypotheses to be tested and questions to be answered and (*d*) a detailed outline for a practical experiment design. The pretracing experiment design comprised: the selection of the study group; the listing of possible sources of information; a plan for orderly tracing; a provision for the collection and recording of information; plans for "controls" and an outline for the analysis of data.

The study was undertaken with the ultimate objective of providing information on the natural course of syphilis according to as many indices as the material would allow.

One of the very significant contributions of this investigation is the information obtained on clinical secondary relapse: 23.6 per cent of these patients experienced this manifestation within five years of discharge from the hospital (males 22.7 per cent; females 24.0 per cent) and of these approximately one-fourth had multiple episodes.

Benign late syphilis occurred in 14.4 per cent of males and 16.7 per cent of females. It was observed as early as the first year after discharge and as late as the forty-sixth year, the majority developing by the fifteenth year. There was some evidence of earlier appearance in females than in males and some suggestion that the probability of development is greater among females.

Cardiovascular syphilis was observed to have developed in 13.6 per cent of males and 7.6 per cent of females, no cases occurring in those infected before the age of 15.

Neurosyphilis did develop in patients who were infected before the age of 15, but not in males infected after the age of 40. In neurosyphilis there was a two to one ratio of males to females (males 9.4 per cent and females 5.0 per cent).

The mortality from syphilis among males was twice that of females, but in neither sex was it an important cause of death. It was second as a cause of death in males and fifth in females, but approximately 90 per cent of deaths were from other causes. There was a definite excess mortality among these syphilitics as compared to the population group from which they came.

No evidence was found to support the idea that either clinical secondary relapse or benign late syphilis has prognostic importance.

This is probably the most comprehensive study of untreated syphilis that has yet been made, and the great mass of data that have been collected will provide the basis for additional contributions to our knowledge of syphilitic infection. This brief review cannot do justice to this monumental piece of work comprising a monograph of some 500 pages,[2] with 83 tables and 12 figures and an annex of 70 pages with 30 tables and two figures. Gjestland's contribution, providing the medical literature the long awaited re-study of the Boeck-Bruusgaard material, will stand as a model of carefully planned and successfully executed field research.

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Infectious Syphilis

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INTRODUCTION

The organism of syphilis, *Treponema pallidum*, is an anaerobe requiring moisture and tissue for survival. It is able to grow and survive despite body defense, but dies quickly away from tissue and moisture. Because of its inability to survive on fomites, we can to a large extent discount as not authenticated most of the reported cases of transmission by indirect means (door knobs, dishes, toilet seats, etc.). The physiologic secretions (vaginal, salivary and seminal fluid) collected in all stages of the disease, both early and late, have been shown in controlled experiments to be noninfectious. The blood, however, may contain the organism in abundance in the early years of infection and at irregular intervals in the later years. From this source the organism may be discharged into the fetal circulation during the early stages of pregnancy or into the vaginal tract by way of the menstrual blood. The organism does not survive in the vaginal tract after menses are completed unless lesions are present from which the organism is repeatedly discharged.

Transmission of syphilis reduced to its simplest terms is a lesion-to-lesion affair except by means of the blood. Unfortunately, the transmitting lesion is often painless, inconspicuous or hidden.

CLASSIFICATION

The untreated disease passes through the following stages:

1. The incubation period of three weeks' duration with limits of 10 to 60 days. During this stage there are no signs or symptoms of infection.

Read at, Syphilis: A Symposium, Vanderbilt University School of Medicine, Nashville, Tennessee, May 17–18, 1963.

* Director, Venereal Disease Control Program, Norfolk, Virginia

2. The primary stage (chancre) of one to five weeks' duration. This consists of the appearance of a lesion at the site of inoculation.
3. The secondary stage appearing two to ten weeks later. This is usually manifested by a generalized eruption lasting about two to six weeks.
4. The latent or quiescent stage lasting two to 20 or more years. This is a stage in which there are no clinical signs or symptoms; the diagnosis is based on the presence of reactive serologic tests and negative spinal fluid examination. Latency is divided into two phases—early, within the first two years of infection, and late, of more than two years' duration. Some prefer to use four years as the dividing line between early and late latency.
5. Late or symptomatic stages (cardiovascular, central nervous system, etc.).

Infectious syphilis includes the primary, secondary and early latent stages. During the stage of early latency there are in the untreated patient periodic relapses to the secondary types of lesions followed by spontaneous healing. This relapsing tendency occurs for the most part during the first two years of infection. Thereafter, in 95 per cent of cases, immunologic changes occur which prevent the appearance of infectious skin lesions but not progression of the organism in other body tissues. Stated in other terms, the stages of primary and secondary syphilis are to be regarded as continuously infectious, and of early latent syphilis intermittently so, depending upon relapse. In the individual case there is no positive end point of transmissibility since relapse has been reported to occur as long as 20 years after the original infection, and in my own experience was seen up to 13 years after the infection was acquired. On the other hand, some patients probably become noninfectious as early as six months after the disease was contracted.

The true incidence of relapse in untreated syphilis is unknown. My experience indicates that much of this relapse may be subclinical or unobtrusive, often consists of only a few lesions, and is of greater frequency than generally suspected.

It would be misleading to assume that the stages of infectious syphilis represent isolated phenomena from the primary through the early latent stages. Rather we should regard these stages as merely representative of different manifestations of the continuous battle between the organism and the body. Latency is merely a convenient clinical description of the stage in which no outward manifestations of this continuing and active struggle are apparent.

Two factors determine the status of infectiousness: (1) the duration of the disease as previously discussed, and (2) treatment with penicillin or other treponemicidal antibiotics which render open lesions spirochete-free within 24 hours.

CLINICAL MANIFESTATIONS

Primary Syphilis

The typical lesion has an eroded surface with serous discharge, is painless, and of raw-ham color (Fig. 1). The primary lesion, however, may vary in appearance from a small erosion (Fig. 2) to a deep ulcer (Fig. 3). At times the lesion is not even eroded but appears as an area of induration (Fig. 4). The lesion is usually but not invariably single, and is accompanied by painless, nonsuppurative, rubbery, satellite adenopathy. The "typical" classically described lesion probably occurs less frequently than the "atyp-

Fig. 1

Fig. 2

Figure 1. A typical appearing primary lesion indurated and erosive with serous discharge.

Figure 2. A pin head sized questionably indurated primary lesion of the frenulum.

Fig. 3

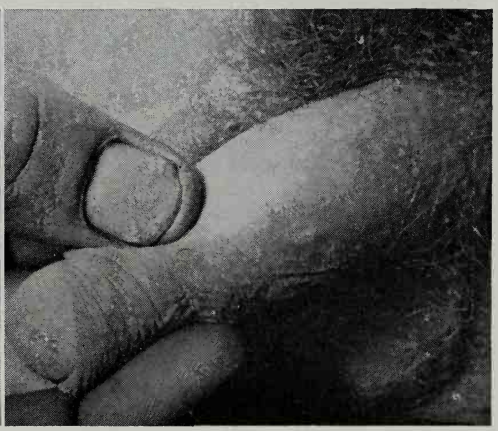

Fig. 4

Figure 3. A deep, painful, ulcerative primary lesion of the anterior thigh.

Figure 4. An indurated nonerosive area of the shaft of the penis. *Treponema pallidum* found after the surface was abraded.

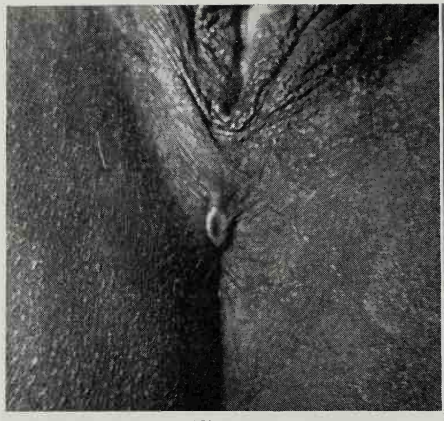

Fig. 5

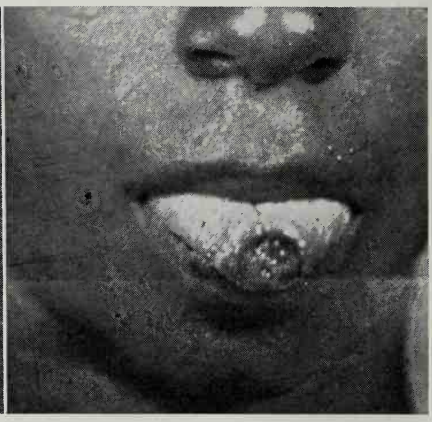

Fig. 6

Figure 5. A perianal primary lesion. Patient refused to allow vaginal coitus for fear of pregnancy.

Figure 6. A primary lesion of the tongue in a homosexual who admitted genito-buccal contact.

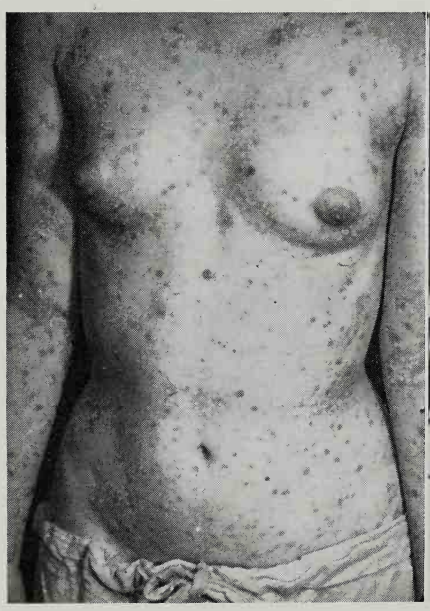

Fig. 7

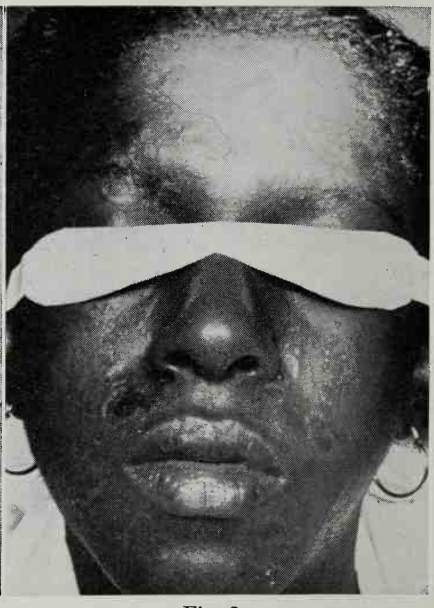

Fig. 8

Figure 7. A typical symmetrical slightly indurated papular secondary.

Figure 8. Hyperpigmented annular lesions with raised depigmented border of the face. This type of eruption is confined almost exclusively to the Negro and is almost pathognomonic of secondary syphilis.

ical" variants. The chancre may be present in an area in which the accompanying adenopathy is inaccessible, such as the perianal region (Fig. 5) or on the cervix where the patient is unaware of its presence. Extragenital primary lesions particularly of the fingers and lips tend to be somewhat painful.

It has been my experience that the physician's index of suspicion drops sharply when the primary lesion is present in an area other than the penis or vulva, and more likely than not, syphilis will not be considered in the diagnosis when the lesion is situated away from the genital region (Fig. 6).

Secondary Syphilis

The secondary eruption may also vary greatly in appearance, and may be conspicuous or inconspicuous. Morphologically the eruption may be macular, papular, papulosquamous, grouped follicular, rarely pustular or nodular, and almost never vesicular. In the oral cavity the lesions are usually eroded and around the genitalia may become vegetative (condylomatous). The typical eruption is symmetrical (Figs. 7 and 8), the atypical and relapsing eruptions often may not be. Usually involved are the oral cavity (Fig. 9), the anogenital area (Fig. 10), and the palms and soles (Fig. 11). The lesions are often slightly indurated and not pruritic. In relapsing secondary syphilis, the lesions tend to be arciform or annular (Figs. 12 and 13).

Secondary lesions covered with a protective epithelial coat on the glabrous skin are not infectious, but become eroded around the anogenital area due to constant moisture. The disease thus becomes primarily venereal from a biologic point of view and not from any malevolent design for punishment. Secondary syphilis is the most highly contagious stage since there are many lesions from which the infection may spread rather than the usual single lesion of primary syphilis. Accompanying generalized adenopathy is a very important sign. Occasionally iritis, patchy alopecia, and sore throat are present. Some patients have slight constitutional symptoms, such as fever or malaise, but usually these are so mild that they are for the most part ignored.

Early Latent Syphilis

Early latent syphilis may be presumed to exist if a history can be obtained of probable primary or secondary lesions within the previous two to four years, or of nonreactive tests within the same time followed by reactive tests. The presence of a standard high-titered quantitative reading (1:16 dils or over) repeated and confirmed as syphilitic by a treponemal test in individuals 25 years of age or less, is also presumptive evidence of probable early latent syphilis if congenital syphilis can reasonably well be ruled out.

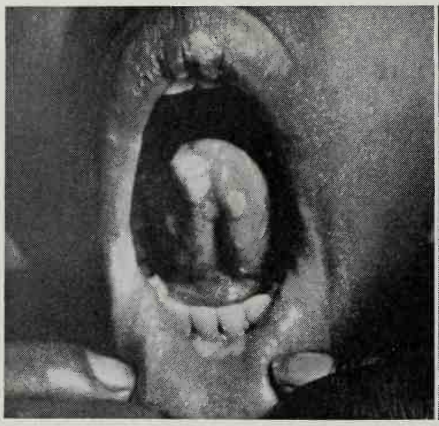

Fig. 9 Fig. 10

Figure 9. Erosive secondary lesions under the tongue (mucous patches).
Figure 10. Condylomata of the anogenital area.

Figure 11. Papular lesions of the palms.

Fig. 12 Fig. 13

Figure 12. Arciform relapsing secondary lesions of the forearm.
Figure 13. Arciform relapsing secondary lesion of the chin.

PLATE I

Fig. 14. Patient unaware of lesions: Two syphilitic papules of the buttock.

Fig. 15. Patient unaware of the lesion. A single syphilitic erosive follicular lesion of the posterior scrotum.

Fig. 16. Patient unaware of lesion. Syphilitic erosive lesion within nostril.

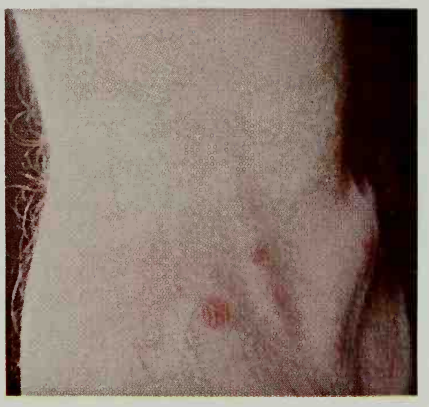

Fig. 17. Patient unaware of lesions. Three erythematous syphilitic papules of the forearm.

LABORATORY TESTS

Darkfield Examination

Properly prepared darkfield examination will reveal the organism in most primary and secondary syphilitic lesions, but the organism may be difficult to find in involuting lesions, in lesions with considerable detritus, or in which topical antiseptics or caustics have been applied. Such unclean or locally treated lesions if soaked periodically in saline for a day or two will, if syphilitic, show organisms. It is best to read the darkfield immediately but this reading may be delayed if the serum is sealed in special capillary tubes to keep the specimen from drying. Experience is necessary for correct morphologic identification of the organism because other genital spirochetes may resemble those of syphilis. In the mouth, saprophytes are present which so closely resemble *Treponema pallidum* that darkfield examination of specimens taken from the oral cavity is usually unreliable. At the present time the fluorescent darkfield technique is being evaluated with some initial success on specimens taken from presumably infectious lesions. The usefulness of the darkfield procedure may thus be extended since this method permits drying of the specimen and therefore delayed reading, as well as differentiation between *Treponema pallidum* and saprophytic morphologically similar organisms. Organisms may be identified in lesions of the glabrous skin by scraping them, or by puncturing satellite lymph nodes, and then examining the serous exudate by the darkfield technique. A positive darkfield permits an absolute immediate diagnosis of the disease.

It is important to remember that the appearance of primary and secondary syphilitic lesions may be modified by small amounts of antibiotic given in inadequate doses for diseases other than syphilis, and if recently given, may eliminate the organism from a lesion that would otherwise show it.

Serologic Tests

The standard serologic tests for syphilis become reactive about one to two weeks after the appearance of the primary lesion or four to five weeks after infection is acquired. Quantitative titers rise rapidly thereafter. By the time the secondary lesions appear the serologic tests are reactive in almost every case and remain so during the latent stage. In the presence of a positive darkfield reading, only the standard serologic tests, including a quantitative test, need be performed in primary and secondary syphilis. In situations in which the clinical symptoms and signs may be confused, and the darkfield examination does not reveal the organism, the treponemal tests are needed for final evaluation. It is important to point out that the titer per se of reactive serologic tests gives no clue as to the status of infectiousness when unaccompanied by clinical information. Doses of antibiotics inadequate for cure of syphilis if given during the incubation period or during the first week of primary syphilis often delay the appearance of reactive serologic tests beyond the usual time.

DIFFERENTIAL DIAGNOSIS

This presentation would inevitably be bogged down in a morass of detail if an attempt were made to go into detailed descriptive differential diagnosis. All of the diseases to be considered have wide variations in clinical manifestations and are adequately described in detail in standard textbooks or articles.

A list of the diseases to be considered in differential diagnosis may be helpful as a guide. In the differential diagnosis of *primary syphilis*, the following diseases are to be considered: chancroid, granuloma inguinale, carcinoma, tuberculosis, lymphogranuloma venereum, trauma, herpes progenitalis, lichen planus and drug eruptions.

Extragenital lesions require, in addition, differentiation from any disease capable of producing a lesion with satellite lymphadenopathy, such as tuberculosis, sporotrichosis, tularemia, herpes, amelanotic melanoma and cat scratch fever.

Diseases to be considered in differential diagnosis of *secondary syphilis* include pityriasis rosea, lichen planus, psoriasis, seborrheic dermatitis, fungous (trichophyton) infection, tinea versicolor, infectious mononucleosis, erythema multiforme, drug eruptions and various exanthemata. Such rare conditions as pityriasis lichenoides chronica, urticaria pigmentosa, sarcoidal mycosis fungoides and granuloma annulare with multiple lesions at times need to be considered. Extracutaneous involvement such as iritis, alopecia and sore throat introduce a host of other etiologic possibilities.

It is important to keep in mind the possibility of co-existence of two diseases, e.g., syphilis and another disease. In addition, one should not fall into the error of assuming that all the presenting pathologic findings are syphilitic because serologic tests are reactive. If presumably infectious syphilitic lesions do not heal promptly following treatment (i.e., within a week) coexisting diseases should be suspected.

EPIDEMIOLOGIC CONSIDERATIONS

The physician's obligation is by no means completed when he diagnoses and treats his patient who has infectious syphilis. If control of syphilis is to be achieved, it is mandatory that contacts, both source and possible spread, be examined. Best epidemiologic results will be obtained if the physician utilizes the specialized skills of health department epidemiologists whose services are readily available. The physician should regard the diagnosis of infectious syphilis as a public health emergency and should contact the health department on the same day that the diagnosis is made. If the patient's diagnosis is primary syphilis, all possible source contacts up to three months prior to the appearance of the lesion should be examined, and if secondary or early latent syphilis, for a 6- to 12-month period

PLATE II

Fig. 18. Patient assumed these papular lesions, which proved to be syphilitic, occurred as result of cutting himself while shaving.

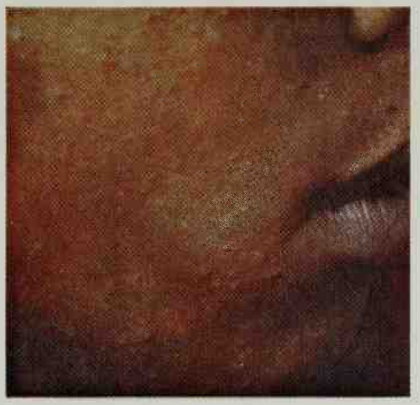

Fig. 19. Syphilitic eruption of face of 5 to 6 days' duration. Patient assumed this was acne.

Fig. 20. Complete examination revealed syphilitic vulvar lesions which patient (Fig. 19) denied existed. Both areas cleared promptly with treatment.

Fig. 21. Raised erosive syphilitic lesion of the nipple.

prior to diagnosis. It is estimated that 40 to 60 per cent of syphilitic patients pass through their primary and secondary stages unaware of or ignoring signs and symptoms as inconsequential. This is the group that it is important to reach if we are to make inroads on the incidence of the disease and only by the epidemiologic approach will they be brought to examination. When darkfield examinations are performed on any lesions present in such contacts, no matter how "atypical" in appearance, we begin to realize the wide variations in the manifestations of infectious syphilis. At times the organism will be found in lesions so "atypical" that even experienced clinicians would not have considered the possibility of syphilis. One shudders to think how often these "atypical" lesions, darkfield positive, are ignored by the patient or misdiagnosed by the physician (Figs. 14 to 21).

Since syphilis is transmitted only by contact with a lesion, the patient with infectious syphilis must have been exposed at least three weeks before (the incubation period) to a contact having an infectious lesion. Therefore, when examining this source contact one should expect to find serologic and possibly clinical evidence of syphilis. In the presence of lesions the diagnosis, of course, can be established promptly by darkfield examination. In the absence of lesions a fast standard flocculation test should be performed. A quantitative VDRL test or one of its modifications can be done by a cooperative laboratory one-half to one hour after the specimen is received. A reactive test in a source contact is considered adequate for the diagnosis of infectious syphilis from an epidemiologic point of view even though no lesions are present. Under these circumstances the diagnosis and treatment of the source contact may be completed in one session. From a clinical point of view, the diagnosis of infectious syphilis is only presumptive in the absence of lesions. If facilities are not available for fast testing or if the contact history is unreliable, treatment may be given purely on an epidemiologic basis. If all the named source contacts show no lesions and have repeatedly nonreactive serologic tests, it is apparent that the epidemiologic information is inaccurate or inadequate.

An individual exposed to infectious syphilis will not show clinical evidence of the disease for at least three weeks and serologic evidence for four to six weeks.

Opinions at this point are divided as to whether or not to treat on purely epidemiologic evidence or to follow this spread contact until a definite diagnosis is established or rejected. The promiscuous group or those difficult to follow are usually treated on an epidemiologic basis, and contact information is obtained and utilized. Every attempt is made to establish a diagnosis. If clinical diagnosis is deemed desirable, serologic testing should be continued for at least three months after the last sexual exposure before the diagnosis is rejected. Diagnosis of infectious syphilis can fairly safely be presumed in a patient who is a contact of a proven case and who shows a rapidly rising titer but no apparent lesions. It should be emphasized that,

if only a definite spread contact (e.g., husband to wife) is brought to treatment, the epidemiologic investigation is incomplete. There must always be a source.

While syphilis is transmitted primarily by heterosexual means—male to female—we have recently become aware of the fact that homosexual transmission may be as frequent among certain groups as heterosexual transmission. In the homosexual group with a venereal disease, there is as a rule a considerably greater degree of promiscuity than in the heterosexual, and the number of contacts named per case is two to three times that named by the heterosexual. Kissing in the presence of oral lesions or abnormal sexual practices (genitobuccal contact) may account for more infection than is generally suspected.

TREATMENT

Paradoxically, the very effectiveness of modern treatment if given in the primary and secondary stages of syphilis, and to a lesser extent in early latency, denies the patient the opportunity to develop significant immunity against the organism. When an infectious type of lesion appears after treatment, this is usually a manifestation of reinfection, rather than relapse. Rigid differentiation between relapse and reinfection is often difficult.

Any of the following treatment schedules given intramuscularly can be expected to achieve a clinical cure in 92 to 95 per cent of infectious syphilitic patients. Fortunately there is no evidence to show that *Treponema pallidum* is capable of developing resistance to penicillin.

1. BENZATHINE PENICILLIN G (Bicillin). 2.4 million units given at one session by injection into two to four sites (2 to 4 cc. per injection).

2. PROCAINE PENICILLIN G IN OIL WITH 2 PER CENT ALUMINUM MONOSTERATE (PAM). 4.8 million units given in doses of 1.2 million units twice weekly for two weeks, or 2.4 million units for the first dose and 1.2 million units for two additional doses with an interval of three to four days.

3. AQUEOUS PROCAINE PENICILLIN G. 4.8 million units given in daily doses of 600,000 units for eight injections.

The first schedule has the advantage that it can be completed in one session.

To check efficacy of treatment in a specific case, the following routine serologic information is essential, in addition to darkfield examination:

1. Pretreatment serologic tests including at least one quantitative reading. For this purpose flocculation tests (VDRL, Mazzini, Kline, etc.) are usually employed.

2. Post-treatment quantitative tests monthly for six to nine months and every three months thereafter for a total observational period of at

least two years. A satisfactory outcome can fairly confidently be predicted if the post-treatment serologic tests show progressively lower titers over a period of three to nine months and remain nonreactive or low titered over the rest of the observational period. Usually the tests become nonreactive or low titered earlier in primary than in secondary syphilis and, if nonreactive before treatment (seronegative primary syphilis), remain so after treatment. The later in the early latent stage that treatment is started the more likely are the quantitative titers to be unchanged by treatment.

Slight fluctuations in the low titered range (e.g., 1 to 4 dils) should not be cause for alarm since such variations may indicate only varying sensitivity of the antigen and/or difference in laboratory interpretation. A variation of significant degree which is confirmed (two-tube dilution or more, e.g., 4 to 16 dils or 16 to 64 dils) indicates either relapse or reinfection and may or may not be associated with the appearance of lesions. In most cases a rapid rise in titer is due to reinfection. If relapse is suspected, the schedule should be doubled, whereas in reinfection the original treatment schedule should be repeated.

For those patients who are sensitive to penicillin, the "mycin" drugs may be substituted. Experience with these drugs is not nearly as extensive as with penicillin. The following schedules are probably adequate:

Tetracycline. Two grams daily in divided doses of 500 mg. four times daily over a period of 15 days for a total of 30 grams.

Erythromycin. Two grams daily in divided doses of 500 mg. four times daily over a period of ten days for a total of 20 grams.

The above schedules need more evaluation before they can be as universally accepted as the penicillin schedules, and represent minimum dosages. Follow-up should include spinal fluid examination. Generally speaking, the "mycins" are not as effectively treponemicidal as penicillin.

COMMENT

I would like to conclude this discussion of infectious syphilis with a plea. An accurate history of possible exposure, onset manifestations, previous verified serologic tests or possible treatment is essential for evaluation. We must realize that infectious syphilis is a disease primarily of signs and very few symptoms. We will have two strikes against us unless the patient is examined completely stripped. To find syphilitic lesions we must snoop around corners so to speak; that is, spread the vulva and buttocks, pull back the foreskin, stretch the scrotum, evert the lips, check the mucous membranes carefully, examine the skin by cross light, pay particular attention to the palms and soles, the sides of the nose, the corners of the mouth, and palpate for the presence of adenopathy. We must realize that the manifestations of primary and secondary syphilis are so varied that the best we can do clinically is to make an educated guess as

to the diagnosis, sometimes with almost 100 per cent assurance and at other times with considerably less certainty. Appropriate laboratory tests are absolutely essential to confirm or reject the clinical impression. Any eruption not typical of a given disease should be investigated for the possibility of syphilis. We should constantly check the impulse to rule out the possibility of syphilis in the well-dressed and well-educated purely on socio-economic considerations, to regard every eruption as syphilitic in the venereal disease clinic and, by contrast, to ignore the possibility of syphilis in other clinics and in our private offices.

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The Importance of Contact Investigation in the Control of Syphilis

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Following the introduction of penicillin as a therapeutic agent and the proven susceptibility of *Treponema pallidum* to this antibiotic, practically all involved in the control of syphilis were convinced that it would be only a matter of time until this disease would be eradicated. Unfortunately treatment alone has not achieved the ideal, and the decline of new cases of syphilis in the United States ended in about 1955. Since then early infectious cases of syphilis have been reported in increasing numbers, from all areas and in practically all social groups.

The belief in penicillin as a method of eventual eradication of the disease was so absolute that there was actually damaging de-emphasis of the epidemiologic methods developed during the past three decades in the control of syphilis. This de-emphasis extended from our medical schools and teaching hospitals to the offices of the practicing physicians and to the departments of health. The marked reduction in financial support for the treatment and control of the venereal diseases extended from the national to the local levels in almost every area of the United States. The attitude of the public has also contributed to this increase in the disease in that the average citizen depends upon penicillin to take care of any of his indiscretions. The importance of venereal disease education, especially for young people, has not been appreciated by some. The number of teen-agers and young adults diagnosed and reported as having primary and secondary syphilis over the past few years is alarming. It was recently stated that more than 50 per cent of all the reported cases of infectious syphilis occurs among teen-agers and young adults under 25 years of age. It is apparent that during the past decade a generation of young people have grown up completely unaware and ignorant of venereal diseases. Almost too late, we are forced by circumstances to recognize the fact that it will take more than a "miracle drug" to control syphilis and the other venereal diseases.

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THE GROWING SERIOUSNESS OF THE PROBLEM OF CONTROL

The seriousness of this problem can be illustrated by a review of reported cases of infectious syphilis (primary and secondary) in the State of Louisiana. The trend for the state and for the City of New Orleans over a period of five years, 1958 through 1962, is shown in Figure 1. The early downward trend of infectious cases reported was followed by a rapid rise and the most marked increase occurred in 1961. It was noted that 32 per cent of the total number of primary and secondary cases occurred in teen-age or young adults, 20 years of age or younger. The number of cases of primary and secondary syphilis reported in the United States from 1957 through 1961 increased by 334 per cent. By comparison, the actual number of reported cases of acute syphilis from 1958 through 1961 in the City of New Orleans increased from 24 to 770. A portion of this increase was due to renewed efforts on contact investigation in the health department.

In a neighboring state, an outbreak of acute syphilis was uncovered primarily among teen-agers. This demonstrates the importance of contact investigation in uncovering an epidemic of syphilis. There were 141 individuals involved. The average age in this group was 19.7 years and the average age of those found infected was 18.4. Thirty-four cases of syphilis and two of gonorrhea were diagnosed and treated. Five of the infected persons brought under treatment attended elementary school. Their ages were 6, 10, 12, 13 and 15 years. Twelve more infected individuals attended high school. The youngest person brought to treatment was a child six years of age having secondary syphilis.

It is evident from the reporting throughout the entire country that the reservoir of infectious syphilis is increasing. The human host, of course, is the sole transmitter of this communicable disease. It is also apparent

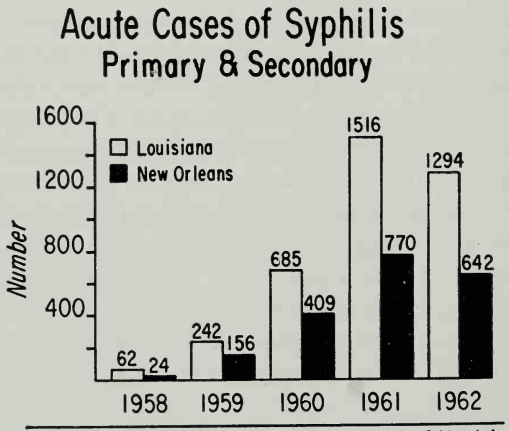


Figure 1.

that determination of sources of infections and the follow-up of contacts have not received the emphasis necessary to control the spread of syphilis.

PRACTICALITY OF EPIDEMIOLOGIC METHODS IN THE CONTROL OF SYPHILIS

The known contacts of individuals with an infectious disease—persons from whom the infection may have been acquired and to whom the disease may have been transmitted—theoretically form the most logical group in which to search for new and unknown cases of any communicable disease.

Since the early studies of syphilis in Europe, it has been recognized as a communicable disease. Ignorance, superstition, moral issues and fear combined to retard the general progress of medical science in finding effective methods of control of the venereal diseases. In spite of these handicaps, within a span of only one century, by clinical observation alone, three distinct modes of transmission of syphilis were proved. These were genital, extragenital and hereditary.

Syphilis, even though it is considered to be a highly infectious disease, is not always communicable. However, like some other chronic infectious diseases, syphilis often remains communicable for long periods of time, though there are even longer periods when the disease is probably noncommunicable to intimate contact.

Epidemiologic studies of syphilis present a series of typical pictures of outbreaks, some small, involving two or three persons, others comparatively large, considering that acquired syphilis is spread almost exclusively by intimate contacts and that congenital syphilis is transmitted only from the pregnant woman to her fetus.

Certain types of epidemiologic investigations in syphilis were for many years considered impossible owing to the modes of transmission which are usually associated with intimate relationships between persons and the lack of effective methods of approach to exposed individuals. In communicable diseases such as tuberculosis, typhoid fever, diphtheria and many others, public health investigators have no hesitancy not only in searching out exposed individuals, but also in keeping such individuals under investigation for a sufficient period of time to determine whether or not they are infected.

It was not until the early 1930's that the same principles of epidemiologic methods, such as contact investigation, were applied in case finding in syphilis. Parran (1932) called attention to the lack of interest on the part of epidemiologists in the use of epidemiologic principles in syphilis control. Munson (1932) demonstrated, by tactful and persistent investigation of contacts of acute cases, that syphilis appears in a community as localized epidemics originating from one or more sources of infection, and that each infected person is potentially a focus of an epidemic. Almost

immediately, the value of such contact investigations were recognized in the control of venereal diseases.

The paper published by Munson (1932) on "Practicability of Epidemiological Methods in the Control of Syphilis," is of historic interest in that he stimulated the use of the epidemiologic approach in the control of syphilis. He stated that the control of syphilis is predicated upon three very distinct factors: (1) early and accurate diagnosis; (2) early and proper treatment and (3) "sole-leather" epidemiology. He was convinced that failure to control syphilis was definitely due to the fact that the cases were not properly investigated along practical epidemiologic lines. Some of the statements made in his published paper deserve repeating here, and I quote: "May I preface some narratives which I wish to give you by stating what may be my feeling concerning epidemiologists and epidemiology? An epidemiologist is that creature who curiously combines a reasonable scepticism and insatiable curiosity with a passion for the truth and has the ability to recognize the truth when it looks him in the face, and with all this has the initiative to apply sufficient sole leather to the job to get the facts. If we are going to control syphilis we must go to work instead of talking about it. If every case of syphilis were investigated and proper attention paid to contacts, as is done with other communicable diseases, it would not be very long before medical students would have difficulty in obtaining clinical material enough for instruction in this disease. There is just one conclusion: Every case of syphilis should have a hard-boiled, determined and bold epidemiological investigation." He then documented his thesis by detailing a number of contact investigations under several different circumstances.

A few individuals following Munson's lead began to use contact investigation as a method of case finding. It was recognized that the facts necessary for an effective epidemiologic attack on syphilis were known. The only thing necessary was a practical application of the information at hand. It was also learned that sources of infection can be determined since only a few persons are usually involved. Elaborate investigation is, however, often necessary in the contact investigation of venereal diseases, and contact investigation requires a considerable amount of skill, tact and patience.

It has been clearly demonstrated over the past ten years that methods to discover reservoirs of infection must be instituted before the control and possible eradication of syphilis can be obtained. These reservoirs are comprised of untreated and inadequately treated individuals with syphilis. Man in this case is his own worst enemy, since man alone is the reservoir and the only source of infection in this disease.

TECHNIQUES OF CONTACT INVESTIGATION

Extensive studies in the epidemiology of syphilis were begun at the syphilis clinic at the Vanderbilt University Hospital in early July, 1937.

Certain preliminary studies had been made prior to this time but the intensive studies in contact investigation were instituted in connection with the establishment of a four-weeks' postgraduate course in syphilis control (Kampmeier and Clark, 1939). This short course of instruction in syphilis control was designed for county health officers and private physicians, cooperating with local health departments, public health nurses and social workers. The syphilis clinic at Vanderbilt Hospital was organized as a special clinic in the Department of Medicine during 1926 and had been concerned only with instruction of undergraduate students and residents (Kampmeier, 1938). The chief objective of this four-weeks' postgraduate course was to provide an opportunity for a period of intensive instruction in diagnostic and therapeutic procedures, with the major effort being placed on case finding, contact investigation, case holding and the broad public health aspects of syphilis control (Frye, Kampmeier and Keller, 1942). Contact investigation had been proved to be one of the most productive methods of case finding by Dr. E. Gurney Clark, the clinic epidemiologist, and others working in the syphilis clinic (Clark, 1940). Each student was given detailed instruction in methods used in contact investigation and each was assigned contacts to trace.

Owing to the importance of the methods of contact investigation at the present time, and the fact that the needs in this area are so important, these methods will be described in some detail.

Successful contact investigation begins with securing the cooperation of the patient who has been found to have early infectious syphilis (Sweeney, 1942). The patient is instructed by his physician concerning the nature of his illness, the treatment necessary, and the precautions which must be followed to prevent the spread of the disease. Usually the examining physician has discussed with the patient the need for contact examination and has explained in detail how the disease may be spread from one person to the others. The physician in his first contact with the patient has laid the groundwork for the obtaining of additional information by the epidemiologist, the public health nurse and the social worker.

Speed is of the essence in contact investigation in syphilitic control. Success in obtaining the names of extramarital sexual contacts of patients with early syphilis depends primarily upon securing the complete cooperation of the patient immediately after the diagnosis is made. The well informed, tactfully handled patient is usually willing to give detailed information. The method of obtaining the names of the contacts has a general basis that must be adapted to fit the individual situation. Patients can usually be persuaded to name and to allow visits to be made to contacts, in most cases, provided they can be assured that their names will not be revealed to the contacts. Visits to contacts can be facilitated by collecting in advance as much information as is possible about that individual or that particular contact. The general method of approach to sexual contacts differs somewhat according to the age, marital status, economic

situation, and position of the contact. The success of the interview with the contact depends largely on securing the confidence of that individual immediately, employing sufficient simple instruction, and in satisfactorily answering the usual question as to who gave his name or her name. Marital problems created by the diagnosis of syphilis in one or both marital partners are frequently serious but can usually be worked out on an individual basis if tactful assistance is promptly given. In most instances, the patient with syphilis can be of assistance in bringing in his own household contacts for examination. It must be re-emphasized here that the period of time between the diagnosis of syphilis in the original patient and the examination of contacts is extremely important in preventing the spread of syphilis.

It has been proved beyond question that, of the various methods of case finding, contact investigation is the most direct epidemiologic approach and offers the best opportunity for discovery of early infectious cases. In contact investigation, attention must be focused primarily upon the patient. The patient is the key to success. Direct questioning as to sexual intimates should follow careful explanation of the disease and adequate consideration of the patient's immediate problems, such as telling the family or interpretations to the marital partner. Names of extramarital sexual contacts are readily obtained when properly sought. The handling of teen-agers and their parents and contacts is a very difficult problem and needs a seasoned interviewer and contact investigator to handle it.

RESULTS—THE FINAL CRITERIA

A few examples of what can be accomplished with contact investigation will help to illustrate the success which has been obtained by this epidemiologic procedure. These examples of case investigations will serve to illustrate the practical aspect of the various procedures which can be used in the application of epidemiologic measures in the control of syphilis.

Figure 2 is of historical interest here since Smith and Brumfield (1933) were among the first to demonstrate the value of contact investigation and to prove the practical application of the epidemiologic method. This is an example of the discovery of a small epidemic, which if not investigated could have led to many more infectious cases of syphilis. Here these investigators presented a new method in the control of syphilis. They also demonstrated that it is practical in all classes of patients to trace the source of infection and to bring the sources under treatment.

Figure 3 is unusual in that the investigation originated as the result of finding a white infant with acquired secondary syphilis. The father, mother and one other member of the household were found infected. Fourteen persons in all were investigated. Ten adults were found to have syphilis, six of whom were in the infectious stage of the disease.

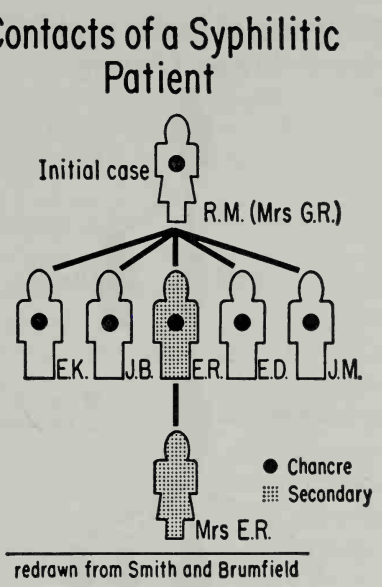
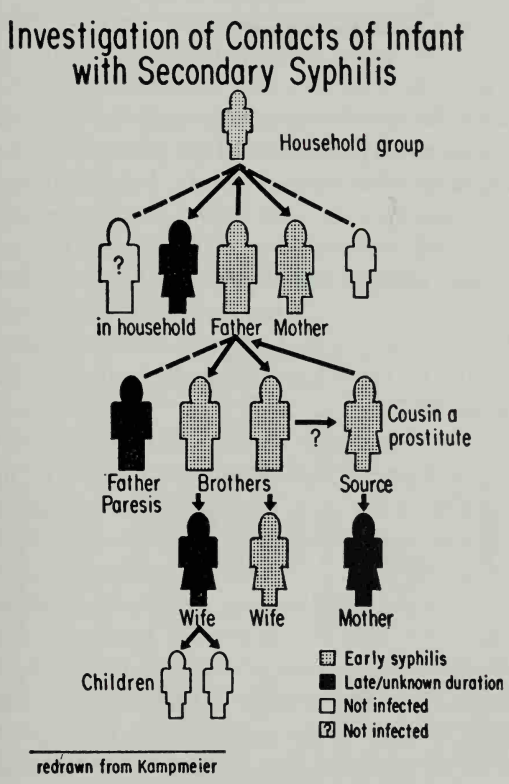


Figure 2.



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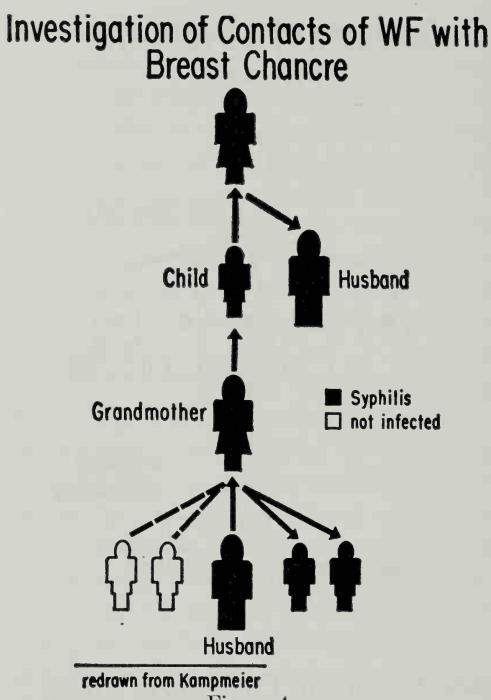


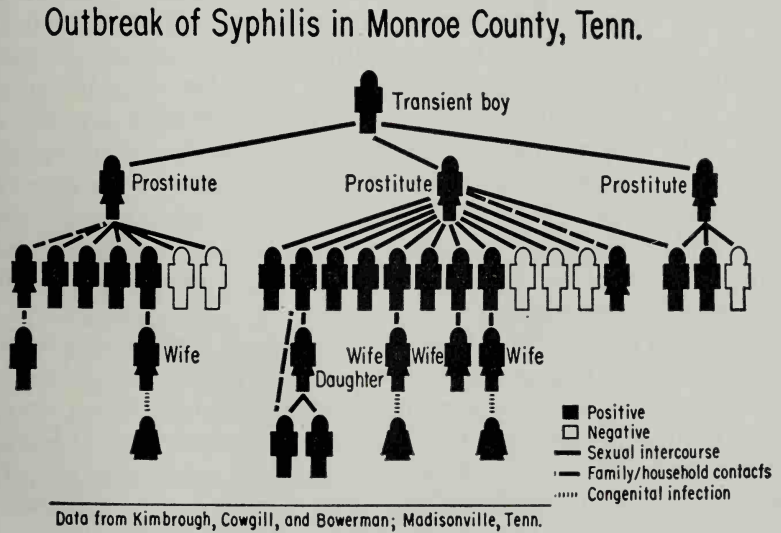
Figure 4.

Figure 4 shows the results of an investigation of contacts of a white female seen for chancre of the breast. This patient had acquired syphilis from nursing her child who had secondary lesions in the mouth. Eight persons were examined and six were found to have syphilis. The grandmother, who was found to have secondary syphilis, had nursed the child. The grandmother had been infected by her husband and her own child had been infected after nursing her. Of the six individuals found to be infected, three were children with acute syphilis, two of whom had become infected through nursing and the third had acquired the disease through "second-hand" chewing gum.

Figure 5 is an illustration of an outbreak of syphilis discovered in a rural county in Tennessee. This investigation helps to illustrate several important points. The index case was that of a young, white male who developed acute syphilis while he was a member of the Civilian Conservation Corp. He was given a few injections of neoarsphenamine and bismuth and discharged from the CCC. He was told upon discharge to report to the county health officer, who would arrange for continuation of his treatment. He failed to do this and, approximately four months later, developed an infectious relapse. He then went to a private physician for treatment. During his relapse, he had sexual contact with three prostitutes, each of whom developed acute syphilis. The physician reported the original case to the health department. The health department personnel and the

practitioner were able to trace 36 contacts, 30 of whom were found to have syphilis. This study illustrates the dangers of inadequate treatment, and the necessity of reporting promptly those persons with acute syphilis who have not had adequate treatment or who leave one area to reside in another. This also illustrates the importance of the practicing physician in the control of syphilis.

Clark (1939) described an epidemic discovered and brought under control in the routine management of patients in the syphilis clinic at Vanderbilt Hospital. A young Negro girl came to the clinic because of early syphilis of the skin and mucous membranes. When she learned the lesions were due to syphilis and were highly infectious and that she had doubtless exposed others to the disease, she disclosed the names of eight young men with whom she had had sexual intercourse. She also agreed to assist in persuading her contacts to have an examination. All of the sexual contacts and six members of her family were examined, either by their own physicians or in the syphilis clinic. Of these 14 persons, nine were found to have syphilis, five of whom were in the infectious stage. A sister was totally unaware of her infectious lesions, and because of this it was a simple matter to develop in her a sympathy for her contacts, who might have no knowledge of the lesions. She designated four sexual contacts, three of whom were found by their own physician to have infectious or potentially infectious syphilis. Subsequent examination of other contacts related to this epidemic disclosed four additional cases of early syphilis and was instrumental in returning two old cases to treatment. In this epidemic, 18 cases of syphilis were found among 32 persons designated as contacts. Most of these were totally unaware of the fact that they had syphilis or that they had been exposed to syphilis.



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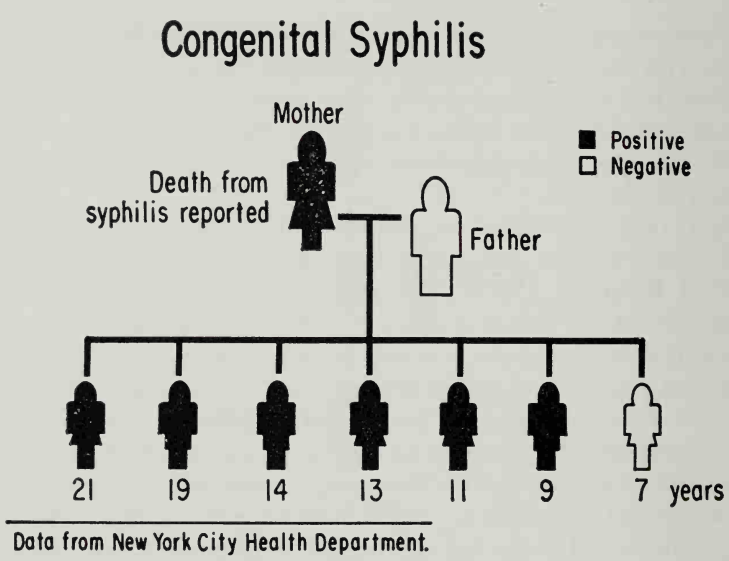

Figure 6.

The results of epidemic investigations conducted by Clark (1940) in the Vanderbilt University Hospital Clinic are of great interest in pointing out what can be and was accomplished when the contacts of acquired syphilis were studied carefully. In a series of 204 cases of primary or secondary syphilis, 387 sexual contacts were named. Of that number, 343 or 88.7 per cent were examined. Of the 343 sexual contacts examined, 258 or 75.3 per cent were found to have syphilis. In the latter group of 258 patients, 213 or 62 per cent were found to have infectious or potentially infectious syphilis. The group of 213 persons included 147 or 42.8 per cent with primary or secondary syphilis, 46 with early, latent syphilis, not previously diagnosed, and 20 patients with early latent syphilis, previously diagnosed but inadequately treated cases. Thus for each 100 original patients, 104 additional patients capable of transmitting syphilis were brought under treatment as the result of the application of epidemiologic procedures. It is obvious that more acute cases of syphilis will be discovered among sexual contacts than will be found among other groups of exposed persons. Among 365 nonsexual family contacts of 520 patients with latent syphilis or late syphilis, ten cases of infectious or potentially infectious syphilis were discovered.

Congenital syphilis must be distinguished from syphilis contracted at or soon after birth. It is an infection acquired during fetal life. Thus every pregnant mother must have a complete examination, including serologic tests for syphilis. In fact, practically all states require by law at least one blood test during pregnancy. Congenital syphilis is preventable and, if the disease is acquired during pregnancy, early diagnosis and treatment will prevent fetal infection. The wisest procedure to follow when infection in

the mother is suspected but unsubstantiated is to examine the mother, both early and late in pregnancy, and to follow the mother serologically and both the mother and child clinically after birth.

Figure 6 illustrates the fact that syphilis may be transmitted from mother to fetus over long periods of time. Fetal deaths from syphilis may occur at any time but are more likely to occur during the early and early latent stages of the disease in the mother. As is illustrated in this family infection, the father was not infected. All but one child born during a period of over ten years was infected. Here again the importance of application of the epidemiologic principles in diagnosis and prevention of congenital syphilis are obvious.

A PRACTICAL PROGRAM FOR THE FUTURE

Early in the campaign against syphilis in the United States, it was demonstrated that the application of epidemiologic methods in the prevention and in the control of this disease is practical. The epidemiologic methods must be applied by official health agencies as a part of the program for the prevention and control of this communicable disease. The medical and public health personnel should be responsible for case investigation. If contact investigators are properly trained, tactful and conscientious, there should be no more difficulty in conducting successfully a syphilis case finding program than there would be in the case of tuberculosis, or any other communicable disease.

There was a period of almost two decades when, because of the difficulties of treatment and follow-up, syphilitic patients came to be handled principally by specialists—the bulk being diagnosed and treated in public health facilities.

Now largely because of the development of penicillin therapy, but for other reasons as well, the pendulum has swung again, and the general practitioner is seeing an ever-increasing proportion of acute infectious syphilis or persons suspected of being infected. The important role of the private physician and his increasing interest in the venereal disease problem is indicated by the fact that in 1958 only 3.2 per cent of all primary and secondary cases were reported by private physicians, the remainder being reported from public health clinics. Two years later, this picture had changed and in 1960 private physicians reported 25.9 per cent of the total.

The services of public health venereal disease investigators, who are especially trained in the technique of interviewing and contact tracing, are available to private physicians in many areas and particularly in larger cities. When we consider that every case of syphilis diagnosed represents at least one additional case, that in the person from whom the infection was acquired, plus perhaps one or more additional persons whom the patient in turn may have infected, we realize the importance of rapid and

thorough epidemiologic investigation and treatment of every known case of infectious syphilis. Only in this way can the chain of infection be broken and this is the area in which the trained venereal disease investigator can be of assistance to the private physician.

The control and ultimate eradication of syphilis can be attained, if the fundamental requirements for its control as an infectious disease are satisfied. Increased awareness of its prevalence, expert application of diagnostic measures, adequate treatment, epidemiologic investigation and professional and lay education, all put to use in one common effort will make it possible to attain our goal.

We are no longer dependent upon investigations to demonstrate the value of contact investigation as a case finding method. Dr. Kampmeier, whom we are honoring today, his colleagues, and his many students, both graduate and undergraduate, have been pioneers in the application of the epidemiologic method in venereal disease control.

We now know the cause and mode of spread of syphilis. We have the means and skills for its diagnosis. We have in our possession an effective therapeutic agent. We know enough about its epidemiology to warrant unusual effort for its control. It has been clearly demonstrated that syphilis cannot be controlled by treatment alone. Let us now shape our program to the problem.

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DISCUSSION

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There are two comments I would like to make concerning Dr. Frye's paper. The first concerns an extension of the technique of contact investigation in the epidemiology of early infectious syphilis and the other concerns the problem which exists in the widespread application of epidemiology to early infectious syphilis.

Contact investigation, which I am convinced has been proved to be a necessary technique in epidemiologic control, becomes an even more productive and effective technique when it is expanded to include the syphilitic patient's friends and social group members. This expansion of contact investigation, which was recently evaluated by eight states in the epidemiology of 1256 early infectious syphilis cases, is known as the *cluster procedure.* This procedure is composed of contact and cluster interviewing and involves three groups of people: contacts, cluster suspects, and cluster associates.

Contact interviewing is especially designed to elicit from the infected patient information which will make it possible to find and bring to examination that group of people with whom the patient was sexually intimate during the period of time in which the disease could have been acquired or spread (contacts) and an additional group the patient feels would benefit from an examination (cluster suspects). The patient may believe

that a person would benefit from an examination for any of the following reasons:

1. The person has or has had lesions similar to the patient's lesions or ones which are suggestive of syphilitic infection. When cluster suspects fitting these criteria are named by an infected patient, one out of every ten examined will be infected and in need of treatment.

2. The person lives within or visits frequently the patient's household and/or is a sexual partner or friend of the patient's sexual partners. Cluster suspects so designated will be infected 3 per cent of the time (one out of every 33 examined).

3. The person is a sexual partner or friend of a previously known syphilitic patient. Cluster suspects so designated will be infected 4 per cent of the time (one out of every 25 examined).

Cluster interviewing is performed on noninfected contacts of early infectious syphilis during the course of the epidemiologic process and is an extension of the contact interview to include persons other than the original patient's contacts and cluster suspects. This type interview should be applied to noninfected contacts, not for the purpose of eliciting their sexual partners per se, but to take advantage of their knowledge about the extent of the disease in their immediate community and social groups, and particularly those known to have been treated recently for syphilitic infection (cluster associates).

Associates obtained from cluster interviewing gave the following results:

1. Persons designated by the noninfected contact as having or having had lesions which are suggestive of syphilis will be infected slightly more than 3 per cent of the time (one out of every 30 examined).

2. Persons designated by the noninfected contact as being sex partners or friends of a previously known syphilitic patient will be infected slightly less than 3 per cent of the time (one out of every 35 examined).

It is apparent from these findings that infected patients and their noninfected contacts have a great deal of knowledge concerning their immediate community and/or socio-sexual group. Therefore, the eliciting of cluster suspects and cluster associates must be considered a necessary and integral part of effective epidemiology.

The obvious problem that exists in the widespread application of epidemiology to early infectious syphilis is the failure of the private physician to report all diagnosed cases.

In 1962, the American Social Health Association, in cooperation with the American Medical Association, the American Osteopathic Association and the National Medical Association, conducted a mail survey of all practicing physicians to determine the number of venereal disease patients being treated by private physicians in a three-month period, April 1 through June 30.

Prior to the mail survey, information compiled from private physician

morbidity reports to the state health departments indicated that the private physician was treating approximately one-third of the early infectious syphilis cases. However, the 131,245 replies to the Survey Questionnaire (71.7 per cent of the physicians queried) indicated that the private physician was treating in excess of three-fourths of the early infectious syphilis cases and reporting only 11.3 per cent of these cases to state health departments.

As Dr. Frye has so ably pointed out, syphilis will not be eradicated until epidemiology is applied vigorously to all known cases of early infectious syphilis. Therefore, an increased effort is being exerted, through individual private physician visitation, through work with national and local medical societies, and through articles appearing in professional publications, to encourage complete case reporting by private physicians.

Late Benign Syphilis (Gumma)

SIDNEY OLANSKY, M.D.*

There has been a tendency on the part of many physicians to omit routine serologic testing for syphilis (STS). Failure to perform these tests as part of the routine examination eliminates one of the most important "suspicion arousers" in a disease where a high index of suspicion is essential. A reactive serologic test for syphilis immediately brings in the possibility of syphilis as an explanation for the signs and symptoms of the patient. Naturally, a reactive STS in itself does not make a diagnosis of syphilis, but it must be ruled out and the reactive STS must be explained. There is no substitute for a good history and physical examination in evaluating any patient, but this is especially true in a patient with a reactive serologic test for syphilis.

For the past few years, early syphilis has been definitely increasing in incidence and we can expect soon to see a rise in late syphilis. In the past year, as a result of routine serologic testing for syphilis, we have been able to diagnose one case of paresis and two cases of gumma which would have been overlooked without the aroused suspicion created by the reactive serologic test for syphilis. In late benign syphilis we are observing a patient who has been previously sensitized to the *Treponema pallidum.*

NATURAL HISTORY

The earliest tertiary lesions seen clinically are those which occur following spontaneous healing of secondary syphilis or inadequately treated secondary syphilis. In the era of treatment with arsenic and bismuth these were considered relapses, and indeed many of them must have been, but with penicillin therapy most patients are treated adequately and these probably now represent reinfection in people previously sensitized to the *Treponema pallidum.* This type manifests as multiple and relatively non-destructive lesions and can be distinguished from secondary syphilis only

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by the failure to obtain a positive darkfield examination. When these lesions heal they leave scars—a most unusual event following secondary syphilis.

The more time that passes between the early disease and the appearance of benign tertiary lesions, the more solitary and destructive the lesions become.

CLINICAL PICTURE

The skin manifestations of benign tertiary syphilis may appear as nodular, nodulo-ulcerative or ulcerative lesions or as tumors breaking down to typical punched-out ulcers or gummas. The host response determines which of these types of lesions presents. With a lesser degree of sensitivity the lesions are more nodular, and with a greater degree of sensitivity they are more ulcerative.

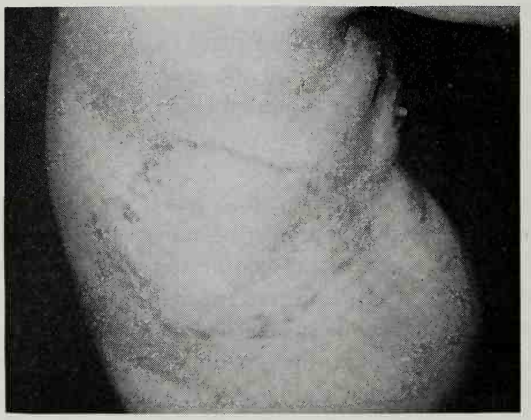

Figure 1. Benign late syphilis (nodular type) showing striking resemblance to tinea corporis.

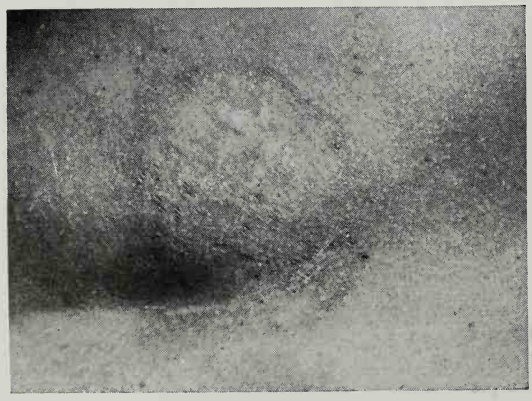

Figure 2. Nodular syphilid resembling tinea corporis. (See also Plate III.)

Figure 3. Nodular ulcerative syphilid resembling tinea. (See also Plate III.)

Figure 4. Stasis ulcer resembling gumma. (See also Plate III.)

The basic characteristics of late benign syphilis are as follows:

1. The serologic tests for syphilis are reactive.

2. Usually the lesions are solitary or few in number except in the so-called "relapses."

3. Asymmetrical distribution of the lesions is usual but by no means invariable.

4. Induration is almost invariable. The lesions usually have "feel."

5. Indolence is characteristic and almost invariable.

6. The lesions tend to be arciform or polycyclic. This feature is a very characteristic one and should arouse suspicion on morphologic grounds alone (Figs. 1, 2 and 3).

7. The lesions are destructive although, at times, this feature may be quite minimal (Figs. 4, 5, 6 and 7).

8. There is a tendency to partial healing without therapy, but spontaneous complete healing is unusual.

9. The scars are atrophic and noncontractile.

10. There is persistent peripheral hyperpigmentation around the border of the lesion.

11. The lesions respond quickly and dramatically to treatment with bismuth, penicillin or other antisyphilitic drugs.

Fig. 5

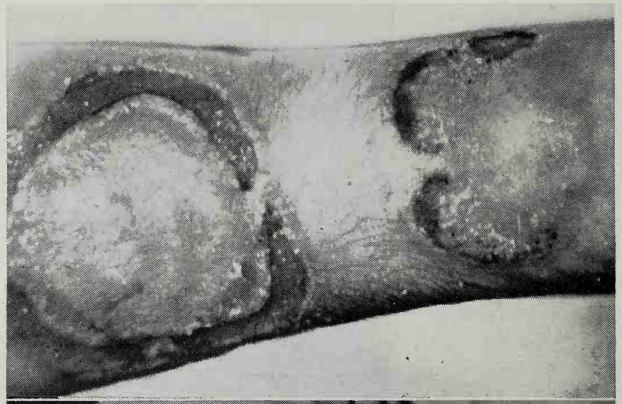

Fig. 6

Figure 5. Ulcerative benign syphilis. The arcuate configuration is very characteristic.

Figure 6. Ulcerative benign syphilis of the elbow.

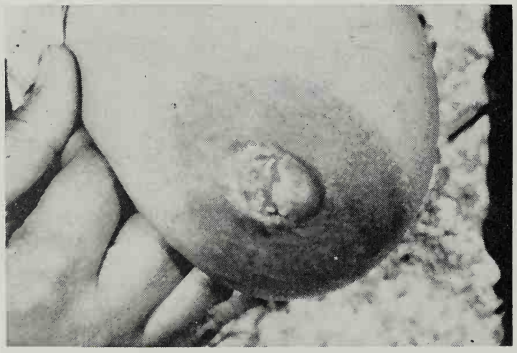

Figure 7. Gumma of the nipple.

PLATE III

Fig. 2 Nodular syphilid resembling tinea corporis.

Fig. 3. Nodular ulcerative syphilid resembling tinea.

Fig. 4. Stasis ulcer resembling gumma.

Fig. 9. Leprosy resembling nodular syphilid.

Fig. 12. Nodular ulcerative syphilid of elbow (Case II).

Fig. 13. Positive STS and history of syphilis resembling gumma (Case IV).

SEROLOGIC TESTS FOR SYPHILIS

The serologic tests for syphilis are always reactive in active benign tertiary syphilis and frequently in quite high titer. There are some reports in the literature of gumma with a nonreactive serologic test for syphilis, but careful analysis of these reports leads to the following conclusions:

1. The diagnosis may be wrong.
2. The result of serologic test for syphilis may be in error. This was especially true with the older serologic tests for syphilis which were low in sensitivity—for example, the old Wassermann test.
3. The lesion may be the result of an old gumma—for example, perforation of the nasal septum or palate. In this instance, particularly in very late congenital syphilis, it is possible for the serologic test for syphilis to become negative if enough time elapses following the appearance and treatment of the lesion. This is similar to the nonreactive serologic test for syphilis observed in an old burned-out tabes dorsalis.

DIFFERENTIAL DIAGNOSIS

Tuberculosis of the Skin. Tuberculosis may resemble gumma clinically and pathologically since both are chronic granulomas. A patient with tuberculosis may also have latent syphilis. The causative organism of tuberculosis can usually be identified in tissue or on culture, which serves to differentiate tuberculosis from late benign syphilis.

Sarcoidosis of the Skin. Clinically, this may resemble tuberculosis of the skin and also gumma but the histopathology of sarcoidosis is fairly characteristic. There is less tendency to destruction and these patients usually have nonreactive serologic tests for syphilis. A therapeutic test with antisyphilitic drugs may be necessary to distinguish sarcoidosis from benign tertiary syphilis, however (Fig. 8).

Leprosy. The clinical lesions of leprosy may resemble syphilis, and

Figure 8. Benign late syphilis (nodular type) resembling lupus vulgaris or sarcoidosis.

Fig. 9

Fig. 10

Figure 9. Leprosy resembling nodular syphilid. (See also Plate III.)
Figure 10. Late benign syphilis resembling discoid lupus erythematosus.

many patients with leprosy have a reactive serologic test for syphilis which is a biologic false positive reaction. The areas of cutaneous anesthesia and the finding of *Mycobacterium leprae* in scrapings from the skin lesions usually can distinguish leprosy from late benign syphilis (Fig. 9).

Sporotrichosis. Sporotrichosis may resemble gumma, although usually these nodules are more painful and inflammatory. A fungus culture revealing *Sporotrichum schenckii* will differentiate it from gumma.

Blastomycosis. This granulomatous lesion may resemble gumma, especially on the leg or on the face. Fungus cultures and direct mounts will reveal *Blastomyces dermatitidis* or yeastlike budding organisms which would confirm the diagnosis of blastomycosis.

Actinomycosis. Actinomycosis may resemble gumma of the lymph nodes in the neck. The pathology and the demonstration of *actinomyces bovis* differentiates it from late benign syphilis.

Psoriasis. Psoriasis may often resemble nodular or nodulo-ulcerative lesions. However, the patient with psoriasis usually has a nonreactive serologic test for syphilis and the pathology of psoriasis is entirely different from that of syphilis.

Discoid Lupus Erythematosus of the Face. Clinically, discoid lupus erythematosus can be confused with late benign syphilis, but the pathology of lupus erythematosus is quite distinct from that of syphilis (Fig. 10).

Tinea Corporis. Tinea corporis may have a striking resemblance to nodular syphilis but a positive fungus culture and a potassium hydroxide preparation will distinguish it from that disease (Figs. 1 and 2).

Factitial Eruptions. Particularly on the legs, factitial eruptions may be difficult to differentiate clinically from gumma. Usually, persons with these eruptions have nonreactive serologic tests for syphilis and the

pathology is that of an acute ulcer rather than the chronic granulomas seen with late benign syphilis.

Sickle Cell Ulcers. These must be distinguished from gummas of the leg. The diagnosis of sickle cell anemia in the patient would serve to establish the etiology.

Epithelioma. Some epitheliomas, particularly those of the face, may be difficult to distinguish clinically from late benign syphilis. Biopsy of the epithelioma is characteristic and would rule out the diagnosis of late benign syphilis. However, an epithelioma may arise on a gumma or on an old healed gummatous scar.

Persistent Erythema Multiforme. This disease may resemble nodular syphilis clinically. The serologic test for syphilis is usually nonreactive and the histopathology is quite distinct from that of late syphilis.

Lymphoma. Cutaneous manifestations of lymphoma, particularly mycosis fungoides, may clinically resemble late benign syphilis. However, lymphoma usually is associated with considerable pruritus and the pathology is quite distinct from that of late benign syphilis.

Granuloma Inguinale. Granuloma inguinale may spread in arcuate fashion and may superficially resemble late syphilis. Frequently these patients also have latent syphilis and a considerable number may well have a reactive serologic test for syphilis. In granuloma inguinale, Donovan bodies can be demonstrated directly from the lesion and the histopathology is quite different from that of syphilis.

Pyoderma Gangrenosum. Pyoderma gangrenosum involving the lower extremities may resemble gumma but is usually much more acute than gummatous ulcers and is frequently associated with ulcerative colitis and with generalized illness not usually seen with late benign syphilis. These patients usually do not have a reactive serologic test for syphilis and the pathology of these lesions is an acute vasculitis.

Granuloma Annulare. This disease may resemble late benign syphilis since it is very asymptomatic and has the morphology of late nodular syphilis. In this situation, the serologic test for syphilis is usually nonreactive and the pathology is distinctive, showing necrobiosis rather than the chronic granuloma seen in late syphilis.

Bromoderma. These vegetative lesions may be quite confusing on the lower extremities. Usually these patients do not have a reactive serologic test for syphilis and the blood bromine level is high.

Leukoplakia of the Mouth. True precancerous leukoplakia has a distinctive pathologic picture whereas so-called leukoplakia associated with late syphilis is quite different. The latter is responsive to antisyphilitic drugs whereas true leukoplakia is not.

Lichen Planus. Lichen planus may present with annular lesions particularly over the penis and may be confused with late nodular syphilis. Lichen planus is, however, frequently pruritic and has a very distinct histopathology. Lichen planus in the mouth may be confused with leuko-

plakia. A biopsy serves to distinguish it both from leukoplakia and late syphilis.

DIAGNOSIS

There is no single test such as the darkfield examination which can unequivocally make the diagnosis of late benign tertiary syphilis. It is suspected when the serologic test for syphilis is reactive and the lesions present are compatible with a diagnosis of benign tertiary syphilis. The histopathology is merely suggestive and cannot be easily distinguished from other chronic granulomas, such as tuberculosis. Often the diagnosis rests on the therapeutic test. Benign tertiary syphilis will respond quickly and dramatically to bismuth, penicillin or other antibiotics such as erythromycin, tetracyclines and chloramphenicol, whereas the diseases which can be confused with syphilis usually will not.

Gumma may appear at any time from one to ten years after initial infection. It should be remembered that all lesions associated with latent syphilis are not gummas. The therapeutic test generally distinguishes the late lesions of syphilis from other conditions that may coexist with latent syphilis.

THEORIES OF GUMMA FORMATION

Hudson and others have proposed a unitarian etiology for all the treponematoses. The morphology of the organisms, the serologic reactions, animal studies and even the clinical expressions are similar, if not identical, in all of the treponematoses (yaws, bejel, endemic syphilis, pinta, etc.). If one can accept Hudson's view, and I do, the late benign lesions of syphilis can best be observed in nonvenereal or endemic syphilis.

In endemic syphilis large numbers of the population are infected, among them many children. If the epidemic persists, these children and others have an adequate opportunity to become re-exposed to fresh organisms after they have been treated or when the disease subsides. Those who have become sensitized by virtue of the previous infection usually have gummas at the site of re-exposure. When these epidemics are controlled by adequate treatment of all known cases, benign tertiary syphilis virtually disappears. Where tertiary syphilis is frequent, there are large reservoirs of *Treponema pallidum* as shown by the occurrence of numerous fresh early cases. Grin has written extensively on the incidence of gumma in endemic syphilis. He reports that in some households benign tertiary syphilis appears at the same time or shortly after other members of the family have fresh infections. He reports a family of 15 people where the eldest son was treated 18 years previously. A fresh infection developed in

three members and some months later in seven other members of the family. At this time, the previously treated eldest son developed a gumma. He concludes that the pathogenesis of tertiary syphilis seems to be repeated exposure in already sensitized people.

Grin feels that benign tertiary syphilis develops for two reasons: (1) reactivation of residual *Treponema pallidum* in sensitized individuals who are inadequately treated, or (2) exogenous re-exposure in sensitized persons who have been adequately treated. There is some experimental support for each of these concepts.

In the Sing Sing study of 1952, 62 volunteers were inoculated with the Nichols strain of *Treponema pallidum*. That this strain was an active one was demonstrated by the fact that eight controls who had not previously had syphilis were all infected, with the development of darkfield-positive lesions at the site of inoculation, and those who were not treated at this point developed lesions of secondary syphilis. Among the volunteers were 26 who had been adequately treated previously, representing late latent syphilitics. Ten of the 26 men in this category developed infection as a result of challenge and one of the ten developed a gumma at the site of inoculation. There was also a group of five late congenital syphilitics who had been adequately treated, and one of these developed a gumma at the site of challenge. The serologic response to the challenge and to subsequent treatment was quite similar in the patients who developed the gummas to that in all the other infected patients in the same categories.

From this observation we can conclude that, under the circumstances of this study, those who developed gummas at the site of challenge were infected and that all of the spirochetes were not destroyed locally. This provides evidence, I believe, that exogenous exposure may produce gumma at the site of introduction of *Treponema pallidum*. This leads to the further conclusion that some patients who have gumma may have been exposed to and infected by individuals with early syphilis. This sequence has been borne out clinically. Since the Sing Sing study was completed, epidemiology on patients with gumma has frequently led to the finding of early lesions in their sexual contacts. This was particularly true if the gumma was in the anogenital region. The Sing Sing study therefore would support Grin as regards exogenous exposure in a sensitized individual as one of the explanations of gumma.

Recently, Collart et al. conducted some studies which may have some bearing on the understanding of gummas. They found *Treponema pallidum* in the inguinal lymph nodes of nine patients who had had syphilis which had been adequately treated several years previously. They demonstrated these treponemes by silver staining techniques. In four cases, part of the lymph node was inoculated into rabbits, and in three, *Treponema pallidum* could be found in the lesions which developed at these sites. In these rabbits, the Treponema Pallidum Immobilization Test did not become positive and the rabbit was technically not infected. Collart and his

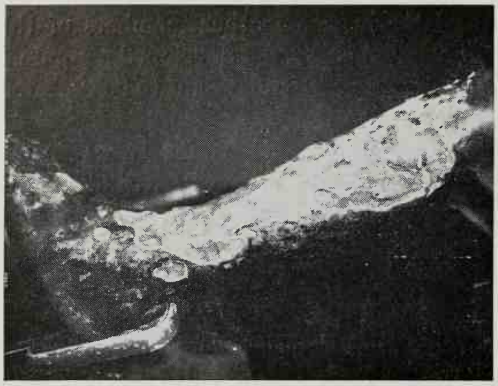

Figure 11. Ulcerative benign syphilis of the leg (Case I)

co-workers inferred from this that the *Treponema pallidum* retained its morphology but lost its virulence. In another study, they inoculated rabbits with *Treponema pallidum* and after two years treated them with benzathine penicillin (Bicillin). One year later lymph nodes were removed from these rabbits, and smears revealed *Treponema pallidum* by silver staining techniques. Transfer of these nodes to fresh rabbits, however, did not produce infection. Cortisone was given to one of these treated latent rabbits and this rabbit developed typical late syphilis. Collart thought that the cortisone upset the immunity sufficiently to allow the spirochete to again become virulent and antigenic. This work would tend to support Grin's feeling about endogenous *Treponema pallidum* and their part in the production of gummas in the inadequately treated individual.

If a high index of suspicion is necessary to diagnose early syphilis, it is perhaps even more so in late syphilis. The following case reports illustrate this fact.

CASE I. J.V., a 70 year old male Negro, had been attending a varicose vein clinic for the treatment of unilateral ulcers of the leg of approximately 18 months' duration. Unna's boots had been applied with great regularity with no real effect on the lesions. The lesions continued to develop in one area as they healed in another. They were asymptomatic and when they healed showed noncontractile scars and hyperpigmentation at the borders (Fig. 11). Since the patient did not respond to varicose ulcer management, it was felt that surgical intervention was necessary and at this time a serologic test for syphilis was made and found to be reactive. He was then referred to the Rapid Treatment Center for the treatment of his blood so that surgery could be performed. Even with the reactive serologic test for syphilis, the possibility of gumma was not considered. The patient was treated with chloramphenicol which was being used experimentally at that time. The lesions healed completely in less than 2 weeks and he remained well for approximately 6 years after therapy, when he was lost to follow-up.

CASE II. J.C., a 65 year old Negro, was admitted to the hospital with a chronic hypertrophic ulcerative lesion over the elbow. He was considered to have a deep fungus infection. Many attempts to culture the organisms of blastomycosis, sporotrichosis, and other deep fungi were made without success. He was skin tested to all of the known fungal extracts with negative results. The possibility of tuber-

culosis was considered and ruled out as were the other chronic granulomas, with the exception of syphilis (Fig. 12). When I was called to see the patient after all these diagnostic studies had been made, it was apparent that the only test not previously done was the serologic test for syphilis. This proved to be highly reactive. Pencillin therapy was administered and produced rapid healing of an ulcer which had been present for approximately 8 months. The lesion was a gumma.

Case III. A 12 year old Negro child was seen with enlarged, nontender lymph nodes in the neck which were draining what seemed to be rather thin pus. Because she was Negro and because of the location of the nodes, tuberculosis was considered to be the most likely diagnosis. However, the skin test for tuberculosis was negative, x-ray of the chest and bones revealed no evidence of tuberculosis, cultures for actinomycosis were negative and ultimately the serologic test for syphilis was performed and was strongly reactive. History at this time revealed that this child had late congenital syphilis. Bismuth therapy was administered and the lesions were completely healed within a period of 3 weeks. The diagnosis was gumma of the lymph nodes of the neck.

Occasionally, what seems to be syphilis turns out not to be, as illustrated by the following case.

Case IV. M.J. was a 60 year old white man with 3 draining sinuses in the neck just above the right clavicle (Fig. 13). The patient was known to have had

Figure 12. Nobular ulcerative syphilid of elbow (Case II). (See also Plate III.)

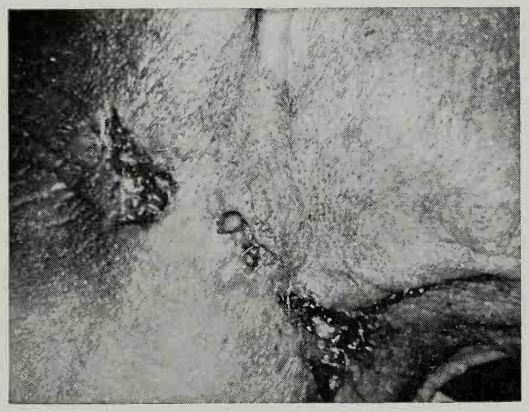

Figure 13. Positive STS and history of syphilis resembling gumma (Case IV). (See also Plate III.)

Figure 14. Benign late syphilis (nodular type) (Case V).

syphilis in the past, had been adequately treated and his serologic test for syphilis was reactive in a low titer. Biopsy from one of the sinuses revealed basal cell carcinoma which responded dramatically to x-ray treatment. It should be mentioned that he had been given penicillin previously on the supposition that these were late syphilis lesions.

CASE V. C.S., a 45 year old white man, was seen in a dermatology clinic with the chief complaint of a persistent eruption previously diagnosed as a fungus infection of the palms of the hands and forearms of 18 months' duration. Physical examination revealed a slightly nodular, hyperpigmented eruption with slight tendency to healing. The eruption appeared in the form of circles and segments of circles and had extended very slowly over the period of 18 months to involve both palms and forearms almost to the antecubital areas (Fig. 14). The lesions were completely asymptomatic. The patient's description was, "I would like to get rid of this rash because when I get into a bathing suit or wear short sleeves, it looks bad. People might think I have a contagious disease." A routine serologic test for syphilis was reactive in high titer. Penicillin therapy melted the lesions away. The diagnosis was, of course, late benign syphilis of the nodular type.

These case histories illustrate only partially the wide range of clinical expressions possible in late benign syphilis which are visible to the naked eye. They support the need for a high index of suspicion and for the performance of routine serologic tests for syphilis in any good medical work-up. All of these patients had reactive serologic tests for syphilis but four of them had lesions of late syphilis and one did not. This emphasizes the need for evaluating the laboratory test results in terms of the whole patient. A firm diagnosis of late benign syphilis, if correct, is a very desirable diagnosis to make because therapy for this is usually much simpler, safer and surer than are the therapies available for most of the conditions from which it must be differentiated.

No mention has been made, so far, of the late benign lesions which are not visible to the naked eye, i.e., visceral lesions. Late benign lesions of syphilis have been reported in practically every organ. Lack of space makes it impossible to go into detail about the diagnostic features of each

of these. However, the diagnostic principles are exactly the same whether the lesions are directly or indirectly visible. The reactive serologic tests for syphilis should alert the clinician to the possibility that syphilis is responsible for the signs and symptoms. If the possibility of visceral benign tertiary syphilis cannot be eliminated, a therapeutic test with bismuth, penicillin, erythromycin, tetracyclines or chloramphenicol will almost invariably provide the evidence needed to prove or disprove the diagnosis of late benign syphilis.

CONCLUSIONS

The diagnosis of late benign syphilis is dependent upon (1) routine serologic tests for syphilis, (2) a high index of suspicion, (3) good medical principles, and (4) a therapeutic test with antisyphilitic drugs. If all the above factors are properly considered, the ability to cure some patients with simple, safe therapy who might otherwise have been considered incurable or doomed will be rewarding indeed.

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The Late Manifestations of Syphilis: Skeletal, Visceral and Cardiovascular

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Beyond the early years of the syphilitic infection with its infectious lesions—the chancre, the condyloma latum, and mucous patches —and the evidences of recurrent spirochetemia as mucocutaneous relapse, neurorelapse, infection of the infant in utero, and the occasional transmission of syphilis by blood transfusion, the clinician turns his attention from these public health aspects of the disease, to the morbidity and mortality of its late manifestations.

The immunopathologic progress of the syphilitic infection from its inception through a subclinical course of latency to end in spontaneous "cure," or of activity to cause death three decades or more after infection offers a series of confusing and unexplained events difficult of correlation. The primary or secondary lesions are characterized by a remarkable infiltrate of plasma cells, lymphocytes and fibroblasts, especially about the small vessels. Numerous treponemes and the same inflammatory infiltrate are found about the capillaries. The secondary lesion tends to be a proliferative process and focal lesions are found in the corium separate from the areas involved in the rash.

The importance of calling attention to the immunopathologic processes of early syphilis is their bearing upon the later manifestations of the disease. Recurrent crops of papules appearing simultaneously with healing of like lesions elsewhere may be characteristic of clinical relapse in the early years of the infection. This suggests that immunity is not humoral, but rather a specific "tissue immunity," with an element of a hypersensitivity reaction or response to the treponeme or a product from it. This poses unanswered questions as to degrees of tissue immunity varying from host to host. It asks for answers to a number of questions: Why does the treponeme

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Figure 1. Darkfield-positive lesion following trauma. The fourth infectious relapse (darkfield-positive in each) in 3 years since the primary penile lesion. (Total treatment included 34,200,000 units of penicillin, 15 injections of Mapharsen and 9 of bismuth. Seronegativity attained after 4 years of positive tests.) (Courtesy South. M. J. *46:* 226, 1953.[1])

become established in the cerebrum of certain hosts during the spirochetemia of the early years of the infection gradually to cause the changes to be recognized clinically after two decades as paresis, having in the meantime carried the sign of active involvement in the spinal fluid? On the other hand, why, in the majority of patients, has the treponeme *not* gained a foothold in the cerebrum at the time of spirochetemia? Why has the treponeme invaded the central nervous system to leave its mark as tabes dorsalis and then "burn out" without treatment? Or, why, in certain of the hosts, has the treponeme been attracted to a continuance of recurrent inflammation and healing in the aortic wall and, why, in others, has this not occurred though all infected have been exposed to spirochetemia? Or, why, in contrast to alternating inflammation and fibroblastic proliferation in some hosts, does the gumma appear in others? This is the lesion in which, presumably, a very few organisms (impossible of demonstration by darkfield examination but proven at times by animal inoculation) incite a massive localized inflammatory response with necrosis and giant cell formation, suggestive of reaction in a hypersensitive tissue. What factors account for this sudden response to a presumed focal syphilitic inflammation 10 or 20 years, or more, after the spirochetemia of the early years of the disease? That this represents a tissue response characteristic of only certain hosts is highly probable because of the frequency with which multiple gummas appear, even simultaneously, in the same individual. Whether biochemical or other immunologic factors play a role in the sudden exacerbation which is the gumma is unknown. Repeatedly, however, trauma seems to be an inciting factor in the development of syphilitic periostitis or osteitis, reminiscent of its role in acute pyogenic osteomyelitis. This recalls the

occasional instances of an infiltrative and ulcerative response to trauma during a time of spirochetemia, as shown in Figure 1.[1]

In considering the late manifestations of syphilis, an understanding of the natural course of the *untreated* infection is essential. If Figure 2 is accepted as portraying the biologic course of infection, it is apparent that, except for rare instances, the late manifestations of the disease appear above the *clinical horizon* only after some eight to ten years following infection to end with death either as the result of syphilitic or other disease. Rosahn,[3] in an intensive study of necropsy material at the Yale University School of Medicine to establish acceptable criteria for the pathologic diagnosis of syphilitic disease in contrast to those of Warthin, has offered figures which are remarkably similar to the Oslo figures appearing in Figure 2 based on Boeck's clinical diagnoses.* (See paper by E. Gurney Clark in this volume.) His material came from 380 syphilitic persons of whom 198 or 52 per cent had received no antisyphilitic treatment. Among these, 77 (39.9 per cent) showed anatomic lesions of syphilis, though only 23.2 per cent of the group died primarily of syphilis. The 106 lesions found in this untreated group were the following: 88 (83 per cent) in the cardiovascular system, 8 (7.6 per cent) in the central nervous system, and ten (9.4 per cent) had gummatous lesions of various organs and cirrhosis of the liver. The remaining 121 patients (61.1 per cent) of the 380 syphilitic persons showed no anatomic lesion of syphilis, though in 80 (40.4 per cent) the serologic test was positive during the last hospitalization, and in 35 (17.7 per cent) it was negative.

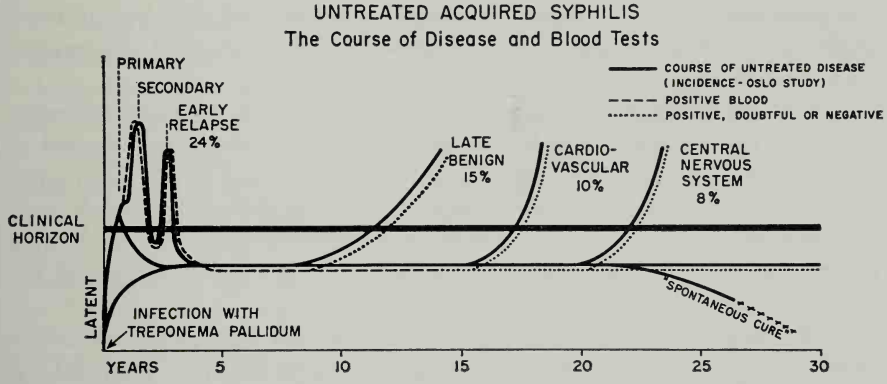


Figure 2. The natural history of untreated acquired syphilis. (Modified from original, courtesy South. M. J. *26:* 18, 1933.[8] Incidence of clinical disease from Clark and Danbolt,[2] J. Chron. Dis. *2:* 311, 1955.)

* Rosahn accepted, in general, the criteria proposed by Nickel: "Definite anatomic changes of syphilis of the central nervous system, vascular tree, bone, and parenchymatous organs including the liver." (Nickel, H.: Statistiche Untersuchungen über die Häufigkeit der Lues am Obductions material. Klin. Wchnschr. *15:* 121, 1936.)

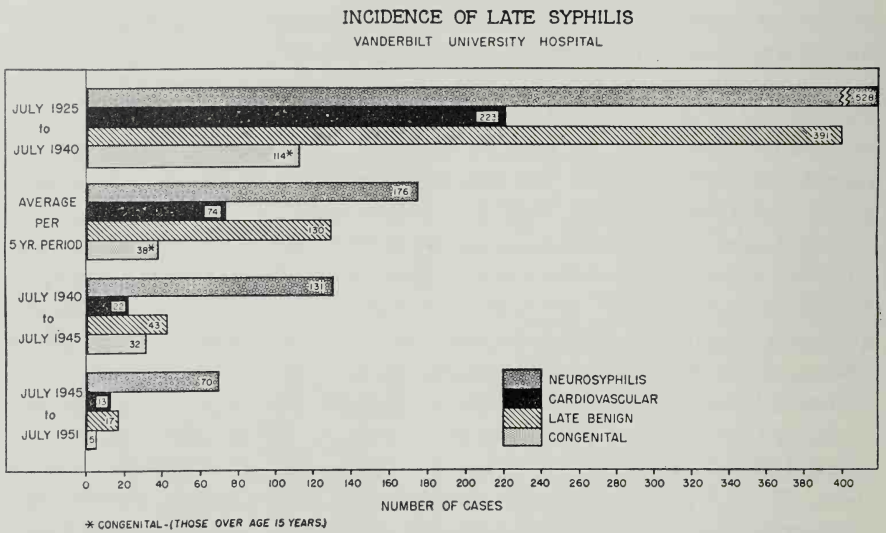


Figure 3. The decrease in the incidence of late syphilis in the Vanderbilt University Hospital Syphilis Clinic. (The experience of the first 15 years could not be broken down by 5-year periods, therefore a 5-year average for this period is used for comparative purposes.) (Courtesy South. M. J. *46:* 226, 1953.[1])

The succeeding discussion will include the late benign manifestations of syphilis exclusive of involvement of the skin, which is the subject of Dr. Olansky's presentation in this volume. Of the generally more serious late manifestations, attention will be directed only to aortitis and its complications, since Dr. Evan Thomas describes so well elsewhere in these pages the serious results of the invasion by treponemes of the central nervous system.

Late manifestations became much less frequent in the years following intensive case finding, which was part of the epidemiologic control of syphilis that began in 1937, not only nationally, but also in the community related to Vanderbilt University Hospital. In the Syphilis Clinic established in this hospital in 1925, and in which an intensive program of case finding and treatment was begun in 1937, the fall-off in the late evidences of the disease is well shown in Figure 3.*

One gains the impression—and it is only an impression—that the incidence of late benign lesions became much less frequent than did the cardiovascular ones. Whether this might be the result of healing of lesions

* These figures represent the incidence of disease in which the diagnosis was made on ambulant clinic patients and does not include diagnoses made on ward patients. Unfortunately figures subsequent to 1952 cannot be included, since with the discontinuance of the Syphilis Clinic that year the syphilitic patients were absorbed into the general medical and/or specialty clinics. Thereafter syphilitic disease was often either not diagnosed and recorded or, if so, did not represent the critical diagnoses made in the former Syphilis Clinic at a history meeting and which included the consensus of three or four clinicians experienced in the disease.

of the hypersensitivity type (the gumma) by incidental treatment with penicillin given for pneumonia, "colds" or other reason, remains one of speculation. (The healed hepatic gumma, for example, leaves no clinical mark.) On the other hand, a similar effect of penicillin upon aortic lesions, if followed by the therapeutic paradox of scar and deformity of the aortic valves or the aortic ring and resultant regurgitation, would not register a comparable decrease in late disease.

LATE BENIGN SYPHILIS*

Historical Note. Adherents of the belief that syphilis was of American origin cite the changes in pre-Columbian bones of American al origines as evidence of osseous syphilis. Similarly those who believe that the treponematoses were indigenous to the Eastern Hemisphere before the discovery of America point to the confusion between leprosy and syphilis in the Middle Ages and cite examples of bony changes in Europe, antedating 1492, thought then to be leprous. Then there are the interesting references to the efficacy of the Saracen's ointment (mercury) which the Crusaders (11th–14th centuries) brought back to Europe from the Near East for the treatment of leprosy! In any event, the first medical descriptions of the late manifestations of syphilis by DeVigo—of the bone, iritis, and nasal ulcerations—appeared in 1514. It is remarkable that these should be recognized only 22 years after the discovery of America. In the following century appeared descriptions of visceral syphilis. The truly scientific analyses and recognition of these lesions were contributed by Wilks and by Virchow in the nineteenth century.

Pathology

It was indicated above that late benign manifestations may represent a proliferative reaction in which, though clinically the patient may appear to be in the stage of latency, there is a chronically progressing inflammatory reaction, often with miliary gummas, replaced by a fibrosing process. This

* It should be obvious that no extensive review of the literature has been attempted in this paper. If bibliographic references seem outdated, it should be recalled that the accumulated clinical knowledge about syphilis has long been well known and that the statistical evaluations pretty much reached their completion between 1930 and World War II. Retrospective studies were begun about a quarter of a century after the discovery of the *T. pallidum* and the first description by Wassermann of a test for the disease. The chiefs of the Syphilis Clinics of the University of Pennsylvania, the Mayo Clinic, the University of Michigan, Western Reserve University and Johns Hopkins University and representatives of the U.S. Public Health Service composed the Cooperative Clinical Group. In a series of papers beginning in 1932 they brought order out of confusion and laid the foundation for modern syphilology. These studies provided the bench mark for the rapid and satisfactory cooperative evaluation of intensive arsenotherapy in the late 30's and early 40's, and then for similar studies upon the efficacy of penicillin therapy between 1943 and 1947.

Major contributions in the past 15 years have been in the areas of the newer therapy, development of specific diagnostic tests, and the sociologic facets playing a role in epidemiology in the disease. References will be made to what I consider the greatest contributions in the clinicopathologic field since the War, the autopsy studies by Rosahn[3] and the statistical re-evaluations of the Oslo cases on the natural history of untreated syphilis by Clark and Danbolt[2] (as reported in this volume).

Table 1. *Distribution of Late Benign Lesions as to Site and Race*

SITE	NEGRO	WHITE
Skeletal (all types)	123	55
Skin	124	47
Upper respiratory tract (nose, throat, larynx)	50	19
Mucous membrane (mouth)	41	19
Eye (all types)	43	11
Visceral (liver, stomach, etc.)	23	14
Lower respiratory tract (?)	2	2
Mediastinum (?)	3	1
Lymph nodes	7	—
Genital tract (female)	4	—
Penis	3	2
Testis	3	1
Skeletal muscle	3	1
TOTALS	429	172

may, depending upon the site and organ involved, leave such scarring as ultimately to end in severe disturbance of function of the affected tissues. Or, the gumma may present a truly destructive lesion, an explosive tissue reaction to a few organisms resulting in a granuloma or tumor which may vary from microscopic size to 5 centimeters or more in diameter. The larger gummas may undergo central necrosis and break through their wall to drain by one or more sinuses. Commonly such a destructive lesion is followed by extensive and disfiguring scar.

Incidence and Distribution

Precocious tertiarism may occur toward the end of the secondary stage of syphilis when the skin lesions, though actually representing relapse as shown by a positive darkfield examination, may begin to take on some of the characteristics of the late syphilid, with its serpiginous progressing border.* Usually, however, the granulomatous lesions show themselves after some eight or ten years to 20 or 25 years, and less commonly 35 or more years, after infection. Table 1 gives the incidence of clinically diagnosed late benign lesions in 6259 patients admitted to the Vanderbilt University Hospital Syphilis Clinic, from its opening in 1925 to 1943. There were 601 instances of late benign syphilis in these patients. It must be re-emphasized that in many patients gummatous lesions are multiple; the table lists the lesions by the anatomic structures involved. Negroes made up 67 per cent of admissions to the Syphilis Clinic; 71 per cent of the late benign lesions appeared in this race. (Patients given the diagnosis of late syphilis on the wards of Vanderbilt University Hospital are not included in this table.)

From the table it will be seen that any tissue or anatomic structure

* Such lesions were not uncommon in patients who were "treatment-resistant" because of irregularity in treatment under arsenotherapy.[4]

may be the site of late lesions. Attention is directed particularly to the identical frequency of late disease in the skeletal system and of the skin. The upper respiratory tract, including the mouth, nose, throat and larynx, also is commonly involved. Of viscera the liver is most frequently affected. (Patients with this lesion are more likely to be admitted directly to the ward service rather than to an outpatient service.) The remainder of the late benign lesions represent rather rare clinical entities.

Syphilis of the Skeletal System

Since the late cutaneous syphilids have been considered by Dr. Olansky, attention will be directed first to disease of the skeletal system which was involved as often as the skin in our clinic. All bones of the skeletal system have been known to be affected by syphilitic disease.

Table 2 presents a radiologic analysis of 67 cases of skeletal syphilis at Vanderbilt University Hospital in which the films were still available and adequate for study.[5] Our study excluded instances of bony involvement in prenatal or in early acquired syphilis, nor did it include cases of involvement of the nasal or palatine bones, or the neuro-arthropathies (Charcot joint). In the survey of 67 patients, 117 bones presented radiographic evidence of disease. This emphasizes the common multiplicity of late lesions in the same patient. (Without a doubt, had the whole skeletal system been examined radiographically in these 67 patients, many more lesions would have been recorded.) From a radiologic viewpoint, it seems probable that the pathologic changes begin usually as periosteal inflammation or gummatous alteration with secondary changes in the adjacent bone as osteitis or osteomyelitis. From the radiologist's viewpoint, the lesions may be placed in three categories. (1) *Periostitis* is characterized by periosteal thickening and localized increased density similar to cortical bone, often as laminated layers or as a diffuse thickening, which may or may not be accompanied by destruction of bone (Fig. 4). (2) *Gummatous osteitis* presents as a destructive or osteomyelitic lesion associated with periosteal and/or osteal changes; there is a varying degree of sclerosis in the neighboring bone (Figs. 5, 6 and 7). (3) *Sclerosing osteitis*, in which a

Table 2. *Bones Showing Radiographic Evidence of Syphilis in 67 Patients*[5]

Tibia	34	Mandible	2
Clavicle	17	Facial bones	1
Skull	15	Sternum	1
Fibula	15	Spine	1
Femur	8	Radius	1
Humerus	5	Metacarpal	1
Rib	4	Metatarsal	1
Ulna	3	Phalanx	1
Scapula	3	Patella	1
Malar bone	2	Ischium	1

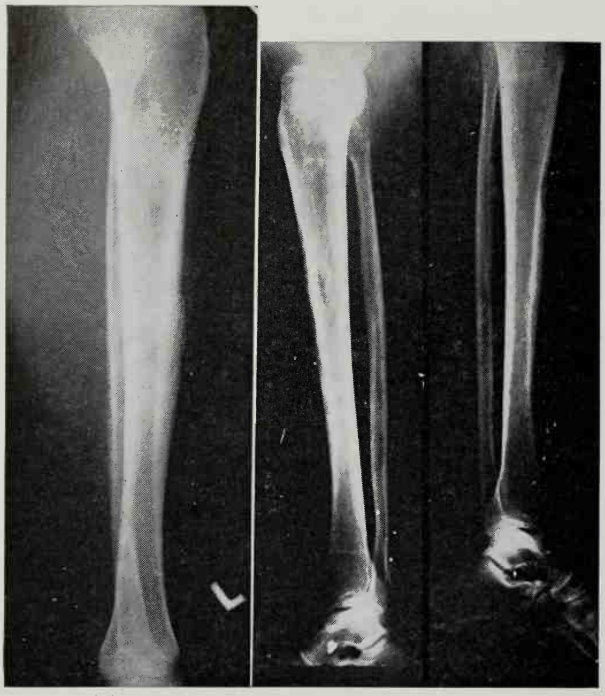


Fig. 4 Fig. 5

Figure 4. Periostitis without destruction. There is localized cortical thickening due to periosteal new bone formation with an undulating edge. (Courtesy South. M. J. *36:* 556, 1943.[5])

Figure 5. Gummatous destruction in both tibias without periosteal reaction; gummas with periosteal reaction involve the fibulas. (Courtesy South. M. J. *36:* 556, 1943.[5])

gumma may be small or obscure, represents a lesion in which the bone shows increased density and is usually accompanied by periosteal change (Fig. 8). The 117 lesions of bone were distributed among these three groups as gummatous osteitis in 73, periostitis in 28 and sclerosing osteitis in 16.

As in all clinical diseases having pathologic changes subject to roentgenologic analysis, there will be a number of patients in whom the radiographic examination is negative. This is not surprising if one recognizes, for example, that sclerosing change in bone must reach the stage which can be shown upon the x-ray film. By contrast, however, it is equally obvious that periosteal reaction insufficient to cast a shadow may yet produce pain, tenderness, and changes in the overlying skin and respond rapidly to antisyphilitic treatment. Therefore an analysis of symptoms of skeletal involvement was made in 106 patients in whom the clinical diagnosis of late osseous syphilis was made.[6] Among these an x-ray diagnosis of gummatous osteitis was made in 36, of periostitis in ten, and of condensing osteitis in eight cases, or radiographic confirmation of the

Table 3. *Symptoms and Signs in 106 Cases of Syphilis of Bone*[6]

SYMPTOMS	NUMBER OF CASES	SIGNS	NUMBER OF CASES
Pain	79	Tenderness	80
Swelling	56	Swelling	55
Nocturnal pain	42	Multiple sites	53
Bony tumor	31	Tumor	48
Stiffness	26	Limited motion	22
Tenderness	20	Redness	15
Trauma	17	Heat	13
Local heat (increased)	11	Sinus	8
Redness	7	Ulcer	4
Immobility	3		
Draining sinuses	13		

clinical diagnosis in 54 patients for a total of 72 lesions. In the 106 cases having a clinical diagnosis of skeletal syphilis, x-ray examinations were either not done or reported as negative in 52 cases, for 61 suspected lesions. The symptoms of the 106 patients with the clinical diagnosis of skeletal syphilis are listed in Table 3. The multiplicity of focal involvement in late syphilis is again well illustrated in these 106 patients since, in addition to multiple bone lesions, one-fifth had other diagnoses of late disease. These

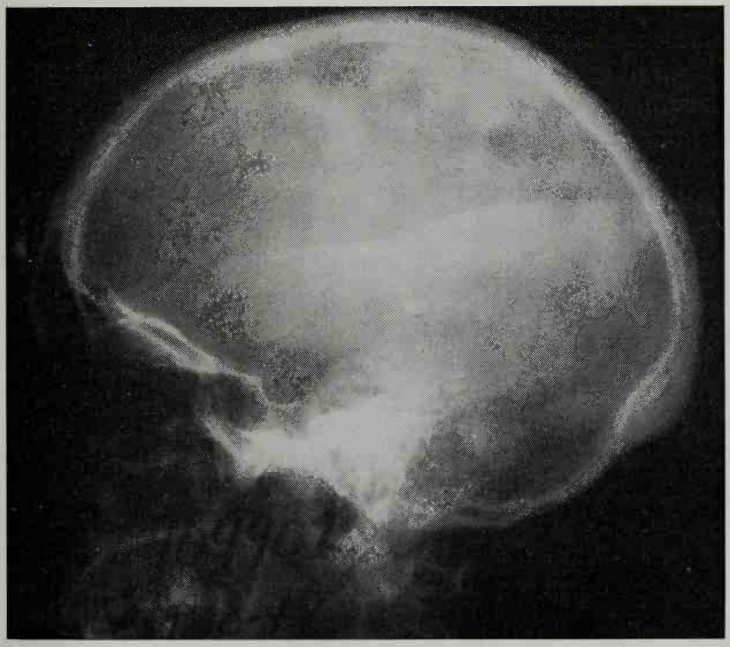


Figure 6. Gummatous osteitis as multiple destructive lesions. (Coincidental with gummatous hepatitis as shown in Figure 15.)

Fig. 7

Fig. 8

Figure 7. Gumma. A destructive cystlike lesion with periosteal thickening. (Courtesy South. M. J. *36:* 556, 1943.[5])

Figure 8. Sclerosing osteitis here shows wavy outlines of dense sclerotic bone. (Courtesy South. M. J. *36:* 556, 1943.[5])

included tertiary involvement of the skin in 11, cardiovascular syphilis in five, neurosyphilis in five, syphilis of the larynx in one and of the testicle in one. In 40 of these patients in whom spinal fluid examination had been done, 11 were found to be seropositive.

Symptomatology. Symptoms of skeletal syphilis result from inflammation of structures permitting only limited expansion. The periosteum is so intimately applied to bone that inflammation must cause severe pain; inflammation in the haversian canals or of the endosteum certainly adds to the pain. For similar reasons the major findings are exquisite tenderness over the involved areas and swelling of tissues overlying the affected periosteum, at times presenting true tumefaction and, not infrequently, redness and warmth of the skin of the area. Weight loss not infrequently accompanies more chronic bony involvement. A prompt response to antisyphilitic treatment indicates the specific nature of the lesion.*

Perichondritis. Comments made upon syphilitic periostitis can be applied to the perichondrium. Syphilis of cartilaginous structures, because of the greater vulnerability of this softer tissue, is likely to result in greater destruction. This is well shown in the occasional instance of involvement

* This statement is based on past experience with medication specific for syphilis only. The relief of an inflammatory process by penicillin does not have the certain connotation as does the resolution of such a process by arsenic and/or bismuth. These drugs offer a diagnosis by therapeutic trial when the differential diagnosis involves other granulomatous disease of bone, such as tuberculosis, or even bone tumor.

of the perichondrium of the cartilaginous nasal septum, the external ear, or of the costal cartilage (Fig. 9).

Differential diagnoses of skeletal syphilis will not be considered in detail since it might be carried too far afield. It should be recognized, however, that syphilis of bone must be differentiated from any other granulomatous disease, of which tuberculosis is the most frequent, as well as from chronic pyogenic osteomyelitis. Osteogenic tumors, primary and metastatic, may be simulated closely by syphilitic disease, and I have known of biopsies done because of the radiologic diagnosis of tumor in the presence of positive serologic tests for syphilis. Osteitis involving the medial end of the clavicle may suggest arthritis of the sternoclavicular joint, as well as erosion by an aortic aneurysm. The latter may be particularly simulated by gummatous osteitis of the sternum. Syphilitic lesions of the facial bones most commonly lead to a diagnosis of retrobulbar tumor, empyema of paranasal sinuses, or carcinoma of the antrum. Syphilitic osteitis of the bony nasal septum (perforation) or of the nasal bones (saddle-nose, Fig. 12) has long been a hallmark of syphilis; less common is involvement of the hard palate with the implied differential diagnosis of carcinoma of the oral mucosa (Fig. 10). The severe and persistent pain accompanying gummatous osteitis of the calvarium not uncommonly has been misinterpreted in terms of disease of the meninges or of brain tumor, and the radiologic examination in some cases may represent difficulties in the differential diagnosis from metastatic carcinoma and multiple myeloma (Fig. 7). Ulceration accompanying periostitis and gummatous osteitis of the tibia is not infrequently considered to represent stasis ulceration

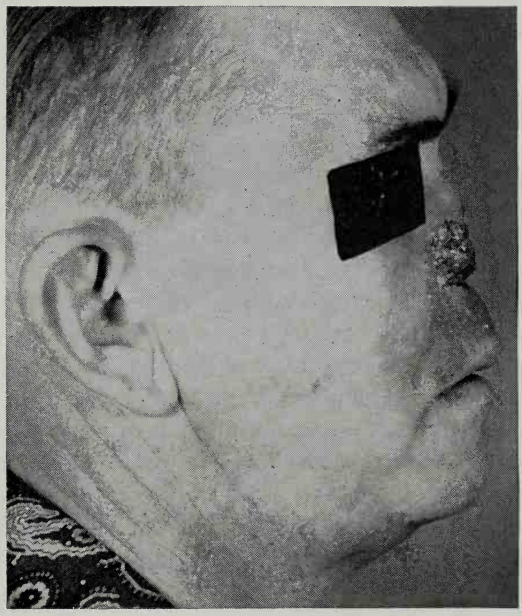


Figure 9. Syphilitic destruction beginning in the cartilaginous nasal septum leading to loss of the tip of the nose.

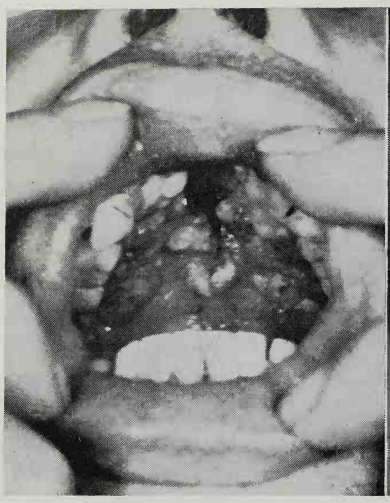


Fig. 10

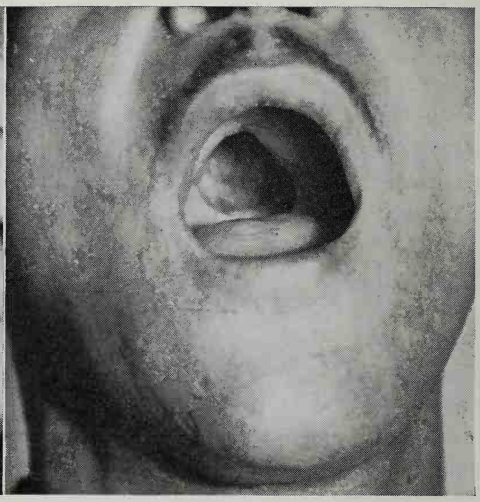


Fig. 11

Figure 10. Syphilitic destruction of the palatal bones. (Kampmeier: Physical Examination in Health and Disease. Courtesy of F. A. Davis Co.)

Figure 11. Large perforation of the soft palate following gummatous ulceration. (Kampmeier: Physical Examination in Health and Disease. Courtesy F. A. Davis Co.)

accompanying varicose veins. Fortunately, involvement of the small bones of the hands and feet is uncommon, and rarely forces a differentiation between one of the arthritides—rheumatoid, tuberculous or gouty—and syphilitic disease of phalanges.

Results of Treatment. Specific therapy is usually followed by complete healing and restoration of bone without x-ray evidence of residua unless the process was a proliferative (sclerosing) one.

Late Syphilis of Mouth and Pharynx

Gummatous disease of structures of the mouth and throat are much less frequent than late lesions of the skin and bones. Among examples encountered in the Vanderbilt University Hospital Syphilis Clinic the most frequent were gummatous disease of the soft palate, tonsillar fossa and posterior pharyngeal wall. Involvement of the hard palate is not uncommon and probably occurs as osteitis or periostitis of the palatal bones since perforation is the usual outcome (Fig. 10). The lips and tongue are rarely the site of gummas.

Clinical Picture. Gummatous infiltration of structures of the throat, soft palate, tonsillar fossae or pharyngeal wall provide the complaint of *chronic* sore throat—weeks or even months of symptoms characterized mainly by discomfort or difficulty in swallowing rather than actual pain, representing a mechanical disability rather than suggestive of the inflammation of acute disease. Examination in a nonulcerative stage shows

thickening or infiltration of the structure involved—the palate, uvula, tonsil, or other structure—with pallor, suggesting edema, but with firmness to the palpating finger. If treatment is not given at this stage, ulceration is inevitable with extensive destruction at times, the extent dependent upon the time of recognition of the cause and proper treatment. Perforation of either the hard or soft palate, deforming scars of tonsillar areas and deep depressed scars of the posterior pharyngeal wall point to a former destructive gummatous ulcer, and are as suggestive of syphilis as a positive blood test (Fig. 11).

Gumma of the lip not infrequently is part of a tertiary syphilid of the face, though it may appear independent of such a lesion (Fig. 12). Gumma of the tongue appears as a tumor deep within the substance of the tongue and if untreated will lead to ulceration (Fig. 13). It responds promptly to antisyphilitic treatment usually with loss of tissue and then often with extensive scar.

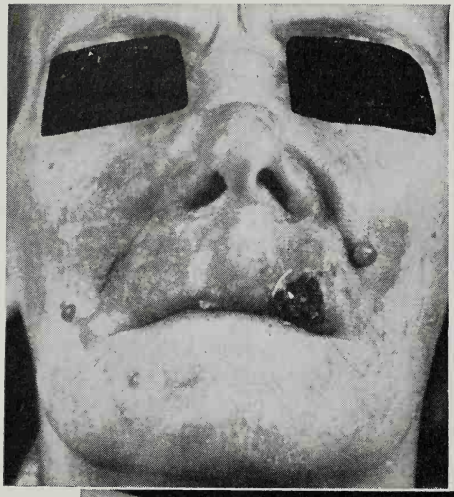
Differential Diagnosis. Differentiation of a chronic tumefaction or ulceration involves but a few lesions, tumor in the main of malignant nature, or of other chronic granulomatous disease, most specifically tuberculosis. Knowledge of the clinical course and the characteristic symptoms and signs of these diseases, including the syphilitic granuloma, and attention given to serologic tests for syphilis, usually point the way to treatment and prompt resolution, which is diagnostic.

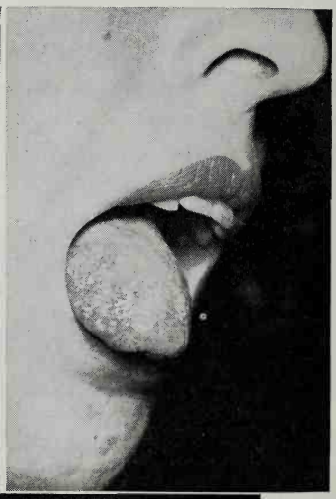
Syphilis of the Respiratory Tract

Serious attention need only be given to the involvement of one structure—the larynx. Gummatous infiltration of the laryngeal mucosa, with or without ulceration, was not an infrequent diagnosis made by the otolaryngologist in former years. The response of these lesions to antisyphilitic treatment is prompt, satisfying and diagnostic. Neglected disease may lead to extensive ulceration, and sloughing of laryngeal cartilages with severe deformity of the larynx. The differential diagnosis involves particularly carcinoma and tuberculosis. The clinical characteristics of these diseases generally permit the experienced laryngologist to differentiate them from gummatous disease. The epiglottis may be involved in the ulcerative process and we have seen it even without the need of a laryngeal mirror, merely by traction on the tongue.

Late lesions of the respiratory passages below the larynx and of the lung are very rare and difficult of confirmatory diagnosis. That they do occur has been documented pathologically. The late lesions of syphilis of the lung may appear either as a solitary tumor or infiltrate rather sharply localized and of several centimeters in diameter, or as a diffuse infiltrative process of major extent. Only rarely is the diagnosis established by pathologic examination; the etiology of the lesion may be questioned if based on its resolution following the use of antibiotics. It is only the disappearance

Fig. 12 Fig. 13





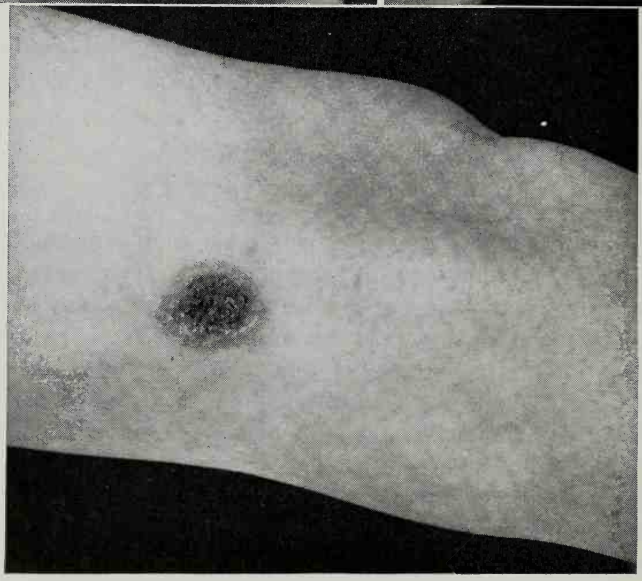


Fig. 14

Figure 12. Gumma of the lip and accompanying involvement of the adjacent skin. (Note the saddle-nose deformity as the result of previous osteitis of the nasal bones.)

Figure 13. Gumma of the tongue. (Kampmeier: Physical Examination in Health and Disease. Courtesy F. A. Davis Co.)

Figure 14. Gumma of lateral aspect of the thigh, above the knee, 3 years after healing of the gumma of Figure 13 subsequent to penicillin. Lesion of thigh was healed by diagnostic bismuth therapy before penicillin therapy was again begun.

of a solitary lesion under bismuth therapy which will permit the presumed diagnosis of gummatous lesion of the lung.

In several patients in our clinic, because of symptoms referred to the respiratory tract, bronchoscopic examination has shown infiltration of the bronchial mucosa, but never have we had success in the specific histopathologic diagnosis of syphilis, rather a description of "chronic inflammatory reaction" of the mucosal biopsy. The response to metal therapy and subsequent resolution of the lesion symptomatically, confirmed in several instances by subsequent bronchoscopic examinations, made it seem probable that just as in the larynx gummatous infiltration of the bronchial mucosa may occur. The certain diagnosis has been impossible in each instance.

Syphilis of the Gastrointestinal Tract

The most common clinically recognized manifestation of late syphilis in these structures has been gummatous hepatitis. Few clinicians have not counted at least one such instance in their experience. It was by far one of the common visceral lesions of the past. Empiricism is usually based on some fact! A half-century ago it was said to be not uncommon practice in the South, with its large colored population and high incidence of syphilis, that if low-grade fever was encountered empiric treatment consisted first of quinine and, if there was no response in the febrile course, mercury and iodides were next exhibited. In the autopsy room of any large hospital in decades past the incidental finding of hepatic gummas or the scarred liver of hepar lobatum was not uncommon, a fact within my experience at the Charity Hospital of New Orleans 30 years ago.

The symptomatology which brings the patient with gummatous hepatitis to the physician are epigastric discomfort and tenderness. More often than not the patient is asymptomatic but becomes aware of a mass in the abdomen, often merely by accident (Fig. 15). Low-grade fever is a common accompaniment, probably the result of the necrosis which commonly occurs in the gummas which, in the liver, are among the largest encountered incidentally at autopsy. In patients with gummatous hepatitis, splenomegaly and anemia are common. The differential diagnosis in the presence of a nodular liver involves more often than not carcinoma, either primary or metastatic, more rarely cysts of congenital origin, and very rarely in this country echinococcal cyst.

Syphilis of the stomach manifested by a mass in the epigastrium and a large ulcer shown radiologically, often with obstruction, has been documented many times and in many hospitals. The symptoms, as might be anticipated, are likely to be interpreted as those of carcinoma or as obstruction accompanying a peptic ulcer, and the radiographic findings commonly seem to substantiate one or the other clinical impression. Most of the reported cases, which have not been inconsiderable in the literature, have

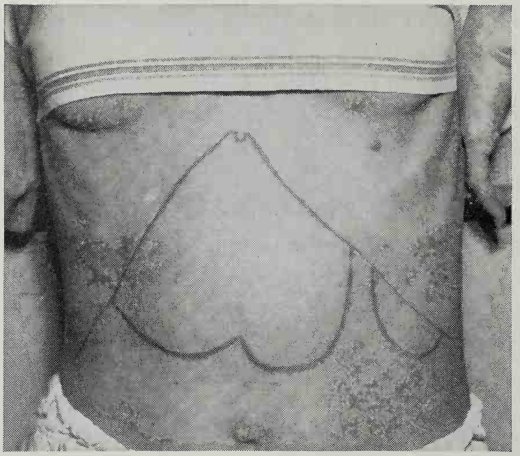


Figure 15. Enlarged liver with large nodules; note splenomegaly. (Kampmeier: Physical Examination in Health and Disease. Courtesy F. A. Davis Co.) Same patient as in Figure 7. Liver receded to the costal margin subsequent to antisyphilitic treatment.

been diagnoses made on surgical specimens. Rarely the esophagus may be involved by a gummatous process, the most common interpretation of clinical and radiographic findings being that of malignancy.[7]

LATE LESIONS OF THE EYES

Iritis. This or iridocyclitis is not unusual as an accompaniment of secondary syphilis, particularly as a relapse phenomenon, often unaccompanied by the other clinical manifestations of rash or lesions of the mucous membrane. However, it also may represent a late evidence of syphilitic infection. The symptomatology of iritis irrespective of its etiology consists of photophobia, pain, and dimness of vision. The characteristic circumcorneal injection and edematous iris again are nonspecific. Adhesions to the anterior lens capsule commonly occur, again irrespective of the cause, and not uncommonly leave a *fixed* pupil, an item of significance at times in the diagnosis of late syphilitic disease of other anatomic structures.

Chorioretinitis. Syphilitic inflammation of the choroid and the delicate overlying retina is not an unusual late lesion. Foci of exudate are obvious on ophthalmoscopic examination; if resolution and healing have occurred, the white sclera is evident with scattered areas of choroidal pigment. The visual loss depends upon the extent and location of retinal involvement and resulting scotomas. Though other diseases produce similar lesions, evidence of former chorioretinitis presents a hint that the treponeme may have passed this way.

Iritis is particularly stubborn to treatment. On the other hand, chorioretinitis responds readily to antisyphilitic treatment, but because of the delicate retinal tissue a Herxheimer reaction may lead to a more extensive functional loss than from the disease per se, untreated at the moment.

Among the cases of late benign disease encountered in the Vanderbilt University Hospital Syphilis Clinic these two manifestations in the eye made up some 10 per cent of late benign lesions.[6] (Primary and secondary optic atrophy and neuroretinitis do not fall into the category of late benign syphilis, representing manifestations of disease of the central nervous system.)

Miscellaneous

The late benign lesions of syphilis of the skin (Olansky), of the skeletal system, the mouth and oropharynx, the larynx, the liver and stomach, and the eyes, already considered, represent the more common sites of the disease.

It may be said, however, that no tissue of the body is immune to the late manifestations of syphilis, and that literally every organ or structure of the body has been reported to be the site upon occasion of either the proliferative or the gummatous lesion. Though involvement in the remaining bodily structures have been documented, they are uncommon. All of the glands, both with exocrine or endocrine function, have been reported to be involved at some time. Syphilitic disease of the pituitary, the thyroid, adrenal, ovaries, testes and pancreas have been proved. (I have seen Addison's disease due to such disease in two patients, proved at necropsy. Gumma of the testicle has appeared in our clinic. Gumma of the thyroid and of the breast tissue have fallen within my experience.)

Late syphilitic lesions of the lymphoid structures, such as of the nodes and spleen, have been reported, and we have seen such involvement of the lymph nodes. Gummas of the kidney have been reported as well as of the urinary bladder. Proliferative disease of the mediastinum was a recognized entity of the past and was encountered by us, if our diagnoses were correct. Gummatous tumors of the brain and of the myocardium have been repeatedly documented in the literature, and encountered occasionally in our own hospital. The spinal cord is rarely involved by a gumma.

Paroxysmal cold hemoglobinuria due to an autohemolysin may occur under a number of circumstances. Among the instances of this uncommon disease, syphilis is a relatively frequent cause, especially of the congenital variety. It responds to antisyphilitic treatment.

Serologic Findings

In Rosahn's[3] autopsy studies at Yale, of the 380 syphilitics coming to autopsy 197 had positive and 116 negative serologic tests at the time of the last hospital admission. Positive tests were clearly more frequent than negative tests in cases in which there were anatomic lesions. Nevertheless, about a fourth of all syphilitics with anatomic lesions at autopsy had negative tests at the time of their last admission, though conversely about one-half of those with positive tests had no histopathologic evidence of syphilis.

Generally speaking, it is to be anticipated that the late benign lesions of syphilis should be accompanied by a high incidence of positive serologic tests. This might be anticipated particularly in the instance of gummas, and especially those which involve parenchymatous organs. It is my experience that widespread involvement of a parenchymatous organ is associated with a positive test in high dilutions. It is also my impression that this is true particularly in syphilitic hepatitis; it is well shown also with the extensive involvement of the cerebrum that is general paresis. On the other hand, a sharply localized gummatous process unaccompanied by widespread involvement of tissues might by chance give a negative test. This we have encountered in syphilitic disease of bone upon occasion. Conversely, however, an apparently negative reaction may represent a zone phenomenon in a blood positive in high titer. This is illustrated in what was obviously osteitis of the tibia due to congenital syphilis. The clinical diagnosis was made with slight confirmatory radiologic evidence. The serologic tests were as follows:

May–August, 1953. A 15 year old Negro boy was studied in the Vanderbilt University Hospital Clinic for "idiopathic" hypochromic anemia (mild) of unknown cause. Kahn and VDRL tests—negative.

June 16, 1954. He entered the emergency room for pretibial pain and tenderness. Temperature 100° F. Kahn—doubtful; VDRL—positive; Wassermann—positive.

June 22. Kahn and VDRL—negative. Radiologist reported bilateral tibial cortical thickening compatible with congenital syphilis.

June 24. Kahn and VDRL—negative; Wassermann—anticomplementary. (Spinal fluid negative.)

June 29. Quantitative VDRL—negative in dilutions 1:2 through 1:32; positive 1:64 through 1:256; negative beyond this. Quantitative Kahn—doubtful in dilutions 1:1 through 1:4; positive 1:8 through 1:256; doubtful 1:512 through 1:2048; negative 1:4096.

Symptomatic improvement followed treatment with penicillin. Variability in positive, negative and doubtful serologic reports and positivity in high dilutions continued through mid-October 1954. Thereafter consistent positivity in VDRL, Kahn and Wassermann tests continued through the last recorded test in December 1957.

Treatment

In general the treatment of late benign syphilis is satisfactory, although in the days of metal therapy an incidence of relapse within the several years after treatment for a previous gumma occurred in some 10 per cent of cases, and irrespective of seroreversal or serofastness.[9] (This was even greater if treatment had been inadequate or erratic.) This has been true only in a few instances of gumma treated by penicillin (Figs. 13, 14). The blood almost always remains serofast.

Treatment with 6 to 9 million units is accepted as adequate treatment. To avoid a Herxheimer reaction in the delicate retina in the treatment of chorioretinitis, I have preferred to resolve the lesion first with aqueous bismuth before beginning penicillin therapy.

CARDIOVASCULAR SYPHILIS

History. As might be guessed, historical descriptions of the complications of syphilitic aortitis began with the descriptions of the gross findings in persons having saccular aneurysms. In the second century A.D. Galen recognized aneurysms resulting from trauma to peripheral arteries.[10] Four centuries later Aëtius wrote on the same topic, but also referred to rupture of an artery without external injury, as seen in the neck, saying ". . . . it very commonly happens to women during parturition, on account of the forceful detention of spirits." Whether this might have referred to aneurysms of the aorta, innominate or carotid is not clear, but if it did, aneurysms in a child-bearing age would without question need to be of syphilitic origin. Fernel, in 1542, gave us the first real description of internal aneurysms of large vessels in the chest and abdomen. Ambroise Paré later in the sixteenth century recognized the relationship of aneurysm to syphilis and related it to the "unction (mercury) and sweat in the cure of French disease."

Good descriptions of various pathologic and clinical aspects of aneurysms appeared during the eighteenth century, and not infrequently related them to syphilis. In 1761, Morgagni wrote the first good description of the gross pathology which characterizes syphilitic aortic disease, describing a small aneurysm of the sinus of Valsalva with rupture into the pericardium, as follows: "That is to say in some places whitish marks of future ossification occurred; in others small foramina, as it were, had begun to be formed; and in still other places were parallel furrows drawn longitudinally; and in this manner was the surface of the artery unequal here and there." In the nineteenth century a number of papers described the various symptoms and signs of aneurysms which have always been the delight of those interested in physical diagnosis, especially before the days of dependence upon the roentgenogram. The first scientific paper attempting to prove that syphilis was the cause of aortic aneurysm appeared in 1875 by Welch,[11] which was protested and unacceptable to prominent English physicians.

Döhle,[12] in 1895, described the hallmarks of the histopathology of syphilitic aortitis. A year after the description of the *Spirochaeta pallida* by Schaudinn and Hoffman, in 1905, Reuter[13] described the organism in the wall of the aorta in aortitis. Thus, through study of aneurysms developed an understanding of the etiology, pathogenesis and clinical manifestations of the complications of syphilitic aortitis.

The basic lesion of acquired cardiovascular syphilis is aortitis. (It is not known to occur in congenital syphilis, and in the Oslo Study[2] was not found even in acquired syphilis if it occurred before age 14.) Though the diagnosis of uncomplicated aortitis is essentially a pathologic one, the clinical recognition of its complications, as aneurysm, aortic insufficiency or stenosis of coronary orifices, usually is quite easy. These are the lesions which make syphilitic cardiovascular disease a disabling and fatal one. Warthin's[14] description, in 1931, of finding treponemes in the myocardium and the pathologic diagnosis of syphilitic myocarditis is accepted by few pathologists. There is a rare case, of which there have been two or three at the Vanderbilt University Hospital, in which it seems probable that myocarditis has occurred in the invasive stage of early syphilis, on the basis of clinical findings, changing electrocardiographic patterns and response to treatment. The etiology in such cases would be difficult to establish.

On the other hand, gummatous myocarditis is a recognized pathologic lesion and well over a hundred cases have been documented in the literature. Most of these lesions have occurred in the wall of the left ventricle and have commonly been associated with bundle branch block; electrocardiographic changes may suggest myocardial infarction. Instances of gumma of the intraventricular septum have been reported, accompanied by complete heart block. (Two such cases have been recognized, with proof at autopsy, at our institution.[15]) Rarely gummatous myocarditis obstructs one or both coronary arteries.

Pathology

The course of syphilitic aortitis most probably represents an early invasion of the aortic wall by the *Treponema pallidum* during the early years of infection when there is recurrent spirochetemia. Just as invasion of the central nervous system may occur early in the secondary stage or as part of secondary relapse, so most probably the vascular structures are invaded either via mediastinal lymphatics as part of the characteristic lymphadenopathy, or directly through the vasa vasorum which are particularly numerous in the ascending and transverse segments of the aortic arch. Aortitis is more frequent in these portions of the arch. (The arterial lesions of syphilis are limited in the main to the large blood vessels, in which there is an arterial blood supply to the wall by vasa vasorum.)

Irrespective of the route of invasion, characteristic lesions of obliterating endarteritis of the vasa vasorum, infiltration by lymphocytes and plasma cells, and necrosis and fragmentation of the elastic tissue in the media, accompanied by lymphocytic exudate and often miliary gummas of the adventitia, present a basic process which goes on over the years and may eventually lead to such a loss of elasticity of the aortic wall as to permit dilatation of the aortic arch or, if there is focal weakening, the development of an aneurysmal sac (Fig. 16). Dilatation of the aortic ring may be accompanied by the characteristic separation and sagging of the valve commissures, and the inflammatory lesion of the aortic wall may involve the valve leaflets as well. These changes in the valves and/or dilatation of the aortic ring explain the aortic regurgitation. Not unusually changes in the aortic wall cause deformity or narrowing of the coronary ostia impairing coronary flow manifested by myocardial insufficiency or by angina. (Some 25 per cent of the patients with aortic insufficiency on my service at Charity Hospital, New Orleans, revealed at autopsy involvement of one or both coronary ostia.) As was indicated in the graphic demonstration of the natural course of untreated syphilis, progressive disease in the aortic wall continues for from 10 to 30 years after infection before the complications of aortitis may become manifest (Fig. 2).

Incidence of Aortitis and Its Complications

It is difficult to evaluate the incidence of complications of syphilitic aortitis from either hospital statistics or private practice. The figures from

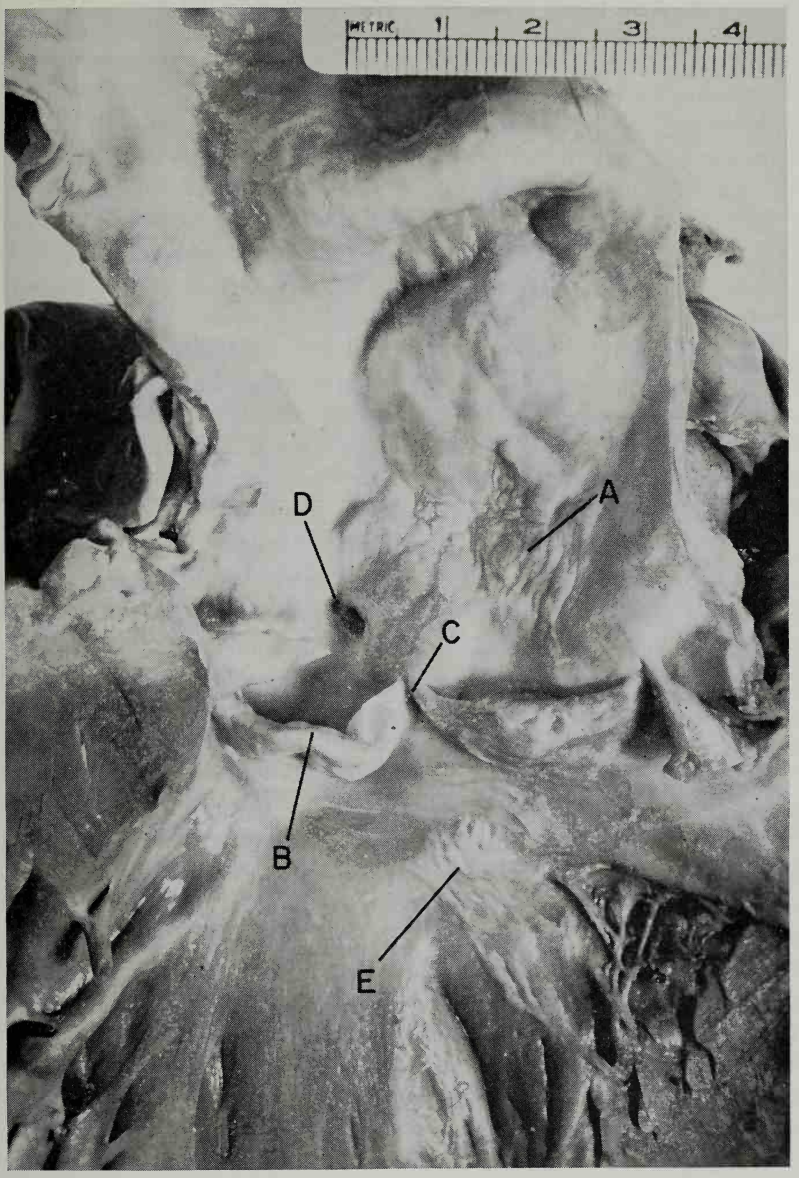


Figure 16. Syphilitic aortitis with the characteristic changes of its complications. This shows the classic dull gray, wrinkled and puckered areas of intima above the aortic valve (A); the thickened, rolled eges of the aortic cusps (B); the lowered attachment of the commissures as related to the level of the coronary ostia, and their separation (C); the narrowed coronary ostium (D); the thickening of the endocardium on the interventricular septum (E). (Kampmeier: Essentials of Syphilology.[6] Courtesy J. B. Lippincott Co.)

Table 4. *Anatomic Findings (Cardiovascular) in 77 Patients with Untreated Syphilis Among Whom 106 Lesions Were Found at Autopsy**

TYPE OF LESION	NUMBER OF LESIONS FOUND			
	In 46 patients dying primarily of syphilis	In 31 patients with syphilitic changes a subsidiary finding	In all 77 patients	
			No.	Per cent
Aortitis with or without valvulitis	26	29	55	
Aneurysm of arch	8	1	9	
Aneurysm of abdominal aorta	1	2	3	
Coronary arteries	4	0	4	
Aortitis of leg vessels	3	0	3	
Cerebral arteritis	2	0	2	
Ruptured aneurysm of arch	9	0	9	
Ruptured aneurysm of innominate artery	1	0	1	
Ruptured cerebral aneurysm	2	0	2	
ALL CARDIOVASCULAR	56	32	88	83.0

* Modified from Rosahn.[3]

the large city hospitals caring for the indigent are weighted by an inordinate incidence of advanced disease, and particularly by a higher incidence of syphilis. On the other hand, the reported incidence of cardiovascular syphilis in private patients is frequently too low, either through misdiagnosis or through dishonest reporting of the cause of death to save the family of the deceased from the stigma of syphilis, or to circumvent riders in insurance policies which exclude venereal disease from the benefits of the policy.

The best figures we have then, are those from the Oslo study by Clark and Danbolt,[2] in which they found the following: in 303 males and 584 females, aortic insufficiency in 7.3 and 3.3 per cent respectively; saccular aneurysm in 3.6 and 1.5 per cent; ostial stenosis in 0.7 and 0.3 per cent, and uncomplicated aortitis found at death in 0.7 and 0.0 per cent respectively.* This provides an incidence of cardiovascular syphilis of 12.3 per cent in males and 5.1 per cent in females, or a total of 10 per cent in 887 persons. It is interesting that this figure is quite comparable to the one accepted for years for the development of complications of aortitis—namely in about 10 per cent of people with untreated syphilis.

Nothing is to be gained by citing additional studies of incidence of aortic insufficiency and/or aneurysms of the aorta from hospital statistics, of which there were many compilations in the past. If one considers rather the evidence as shown at autopsy that uncomplicated aortitis does exist, as pointed out by Rosahn and others, and that the complications of aortitis—aortic regurgitation, saccular aneurysm and involvement of the coronary ostia—may occur, enough has been said for this discussion (Table 4).

*See paper by Clark and Danbolt in this volume.

Clinical Considerations

Uncomplicated Aortitis. Much has been written about the possibility of recognizing this condition upon physical examination, with emphasis particularly upon changes in the aortic second sound. In spite of a long interest in the details of the physical examination, I have never thought that the diagnosis of uncomplicated aortitis is possible by physical means alone. Though aware of changes in the aortic second sound, it has been impossible for me to accept their diagnostic specificity. An analysis was made of the findings recorded in the clinical records of 33 cases of uncomplicated aortitis as diagnosed at necropsy among 168 syphilitics, on whom postmortem examinations were done at Vanderbilt University Hospital.[16] Half of these 33 patients had had no symptoms of cardiovascular disease; in the remaining half there was pathologic evidence of cardiovascular disease which offered a better explanation of symptoms and signs than did uncomplicated aortitis. By contrast with these, among the 168 syphilitics were 30 without pathologic evidence of aortitis, but in whom other cardiovascular disease accounted for a greater number of the symptoms and signs which have been considered to point to a diagnosis of uncomplicated aortitis. White and Wise[17] and others have agreed in this attitude that the diagnosis of cardiovascular syphilis in the absence of aortic regurgitation, aneurysm or narrowing of the coronary artery is for all practical purposes impossible. Even controlled x-ray examinations by fluoroscopy and films of men having late latent syphilis have been unrewarding attempts at an early diagnosis of uncomplicated aortitis. To the contrary, Rich and Webster,[18] in reporting upon the natural course of aortitis in 141 patients, believed that the clinical diagnosis can be made.

Aortic Insufficiency. As was indicated on the graph, the most common complication of syphilitic aortitis manifests itself from 10 to 20 years after infection (Fig. 2). In the past most cases appeared between the ages of 35 to 50 years in white patients. Among Negroes the age incidence was somewhat earlier because of earlier sexual maturity and an earlier age incidence of infection.* Many authors have pointed to the possible effect of heavy labor in the development of the complications from syphilitic aortitis, speculating as to the part played by the Valsalva effect of lifting and other arduous occupations. All studies of the incidence of aortic insufficiency and aneurysm point to a greater frequency in men than in women. Cochems and Kemp[19] reported an incidence of serious cardiovascular syphilis in 14 per cent of those doing heavy labor and in only 8.7 per cent of those in

*It is the duration of the disease and not the actual age which is significant, a fact to be borne in mind in coming years because of the current higher incidence of syphilis in teen-agers than in past decades. As this untreated group moves into the second decade of its infection, the complications of aortitis may appear at an earlier age than in past years. However, it must be recollected that in the Oslo Study cardiovascular disease did not occur if syphilis was acquired before age 14 which, along with the absence of aortic disease in congenital syphilis, points to some unexplained immunity of the large blood vessels to syphilitic invasion in youth.

sedentary occupations. In our study of 163 patients with syphilitic aortic insufficiency at Vanderbilt University Hospital among 2951 cases of late syphilis, we believed that the 91 instances in Negro males, 37 in Negro females, 27 in white males and eight in white females emphasized the probability that heavier work was a factor in the development of this complication of syphilitic aortitis.[20] Though pointing out the difficulties of proving the untoward effect of heavy labor, Webster and associates[21] believe it to be a probable etiologic factor.

The physical findings of aortic regurgitation will not be considered in detail in this discussion. The characteristics of the murmur, its radiation and attendant physical, radiologic and electrocardiographic changes are fully described in the standard reference books on internal medicine or physical diagnosis.

It is worthy of note that in all reported studies on this complication of aortitis a certain number of diagnoses are made in the asymptomatic stage. (In our series of 163 patients the murmur was found incidental to a routine examination and in an asymptomatic phase of the disease in 15 per cent.) It is also significant that not infrequently the clinician, as he follows the course of the patient, will record progression of aortic regurgitation (in contrast to that of rheumatic origin) with increasing intensity and more extensive radiation of the murmur, widening of the pulse pressure, an elevation of the systolic pressure and depression of the diastolic phase, and the gradual development of the peripheral manifestations of a widening pulse pressure. The fluoroscopic demonstration of increased pulsation and/or dilatation of the ascending arch is common. The development of anginal episodes as the disease progresses in not infrequent, probably as much the result of decreased coronary flow secondary to the ill-sustained intra-aortic pressure during diastole, as the narrowing of the coronary ostia commented upon above.

Prognosis in syphilitic valvular incompetence is variable. In patients in whom the diagnosis is made before subjective symptoms develop, and especially in the younger group, the prognosis is relatively good, life extending beyond ten years in a third of the patients.[21] On the other hand, it seems that in many of those who have developed symptoms, death occurs within three years from the onset of symptoms.[20] There is no good evidence that antisyphilitic treatment prolongs life in those who have established aortic regurgitation. (Treatment of the complications of syphilitic aortitis is *prophylactic*—the treatment of latent syphilis, and thus aortitis, before complications develop.)

The *differential diagnosis* in the main involves the differentiation from aortic insufficiency of rheumatic origin, particularly intriguing if the mitral diastolic murmur of the Austin-Flint variety accompanies syphilitic aortic regurgitation, thereby simulating the combined rheumatic lesions of mitral stenosis and aortic insufficiency. Only rarely do diastolic murmurs resulting from longstanding and marked hypertension or calcific aortic valvular

disease pose diagnostic problems in the patient aged 35 to 50. Again the details of differential diagnosis will be found in the standard texts on medicine and physical diagnosis.

The accompaniment of cardiovascular syphilis by cardiac disease of rheumatic, congenital or arteriosclerotic origin is described periodically. The complication of atrial fibrillation points to a nonsyphilitic factor in the apparent heart disease. With extension of life expectancy the recognition of syphilitic heart disease is becoming more frequent in the elderly.[24]

Stenosis of the Coronary Ostia. As was implied above, if syphilitic aortitis involves the coronary ostia with narrowing of one or both orifices, deficient blood flow may lead to some degree of mycocardial ischemia, reflected as angina. This condition is to be considered in the young syphilitic who has angina but does not have hypertension or other evidence of myocardial disease. An absolute diagnosis is difficult. Clinical manifestations as a result of such syphilitic disease may either be ameliorated as a result of antisyphilitic treatment, or may actually appear as a Herxheimer effect—a localized exacerbation of the process immediately following antisyphilitic treatment.

Aortic Aneurysm. True aneurysm as the result of syphilitic aortitis in most instances is of the saccular type, a circumscribed bulging of the wall of a vessel growing to a sac connected to the lumen of the artery usually through a definite ring; less commonly there may be a fusiform dilatation of a portion of a vessel, more often of the aorta. (Dissecting aneurysms are not of syphilitic origin.) In this country aneurysms generally have been considered to have about one-fourth the frequency of syphilitic aortic regurgitation, though in the Oslo series of untreated syphilitics saccular aneurysm occurred about one-half as often as aortic regurgitation, in both sexes.

Saccular aneurysms of the ascending arch of the *thoracic aorta* are associated with a higher incidence of aortic regurgitation than are those of the transverse or descending arches, because of the frequency of aortitis of the ascending arch. My study of 633 saccular aneurysms of the thoracic aorta again emphasizes the probable role of occupation as a predisposing factor in the development of this complication of syphilitic aortitis.[22] It reflects itself in the higher incidence in the male sex as compared to the female (6:1), and also at an earlier age in the Negro patient than the white suggesting probably infection at an earlier age, as well as a higher frequency of heavy labor in the Negro race. (These were the findings among the patients admitted to Charity Hospital (New Orleans) in the earlier decades of this century.) The highest rate of incidence in both Negro men and women appeared between ages 36 and 45. In white men the peak incidence appeared between ages 46 and 55, and in white women an equal incidence in this decade and in the decade 56 to 65.

The clinical diagnosis of aneurysm of the thoracic aorta is usually not difficult in these days of the almost daily use of the x-ray in diagnosis.

Earlier the diagnosis of aneurysm commonly offered the greatest test of clinical acumen in taking the history, doing the physical examination and their interpretation. The wide spectrum of clinical manifestations based on history and physical examination may be summarized by imagining a pulsating tumor varying in size from a few centimeters to 15 or more centimeters in diameter and in intimate relationship to the vital structures in or adjacent to the mediastinum. If one recognizes the structures which might be affected by pressure, as the trachea, major bronchi, lungs, esophagus, pulmonary arteries, vagus and sympathetic nerves, laryngeal, recurrent laryngeal and intercostal nerves, the diaphragm, and indirectly the stomach, one can imagine the whole possible gamut of symptomatology resulting from an aneurysmal sac (Fig. 17). One may add to this the erosion of bony structures by the pulsating mass of the vertebra (with involvement of the spinal roots), ribs, clavicle and sternum (Figs. 18 and 19). Though the roentgenogram usually makes the diagnosis, it is well to recall that a small aneurysm, not demonstrable, may yet impinge upon a vital structure at some strategic point to produce symptoms; even large aneurysmal sacs may be missed if there is pulmonary consolidation, or pleural effusion.

Aneurysms of the *abdominal aorta* are much less frequent than those of the thoracic aorta. They occurred only about one-tenth as often in the Charity Hospital series. Those of syphilitic origin arise characteristically above the origin of the renal arteries. The symptoms result from pressure either upon portions of the gastrointestinal tract, with disturbance in function, or from erosion of the upper lumbar spine with pain from involvement of the respective nerve roots. In a study of 73 patients a palpable pulsating tumor was found in 47, or 60 per cent of cases. The mass may lie high under the diaphragm and then may not be found by palpation. The high location of the syphilitic aneurysm is well demonstrated in 18 instances in which erosion of vertebrae was shown by the x-ray. The vertebra most frequently involved is the first lumbar, and the least frequent the eleventh dorsal and the third lumbar, with equal incidence of involvement of the twelfth dorsal and second lumbar vertebrae. With good lighting and careful inspection, pulsation may be recognized posteriorly to the left of the spine just below the level of the twelfth rib.

The *prognosis* in aortic aneurysm is gloomy, death occurring commonly within a matter of months after the development of symptoms and establishment of the diagnosis. Only rarely does one encounter calcification in the laminated clot which is so characteristic of the saccular aneurysm, and thus "healing" of the lesion. In only several instances have I seen the progression of an aneurysm halted for years by a deposit of calcium.

Differential Diagnosis. It has already been said that the diagnosis of syphilitic saccular aneurysm of the thoracic aorta can be made with relative ease by the x-ray examination, and that probably today most are discovered merely through the routine use of the x-ray. For the interested

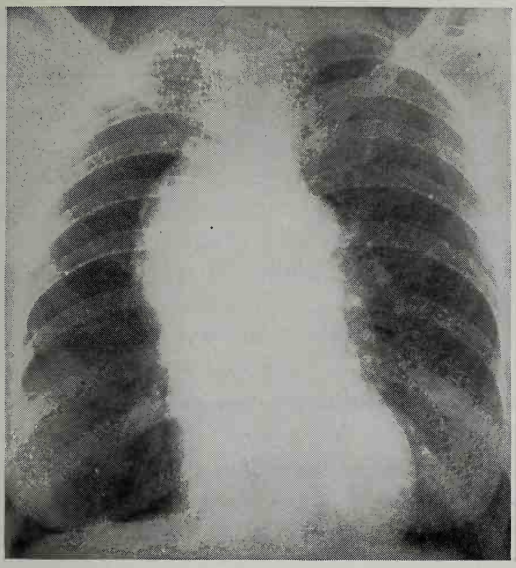


Fig. 17

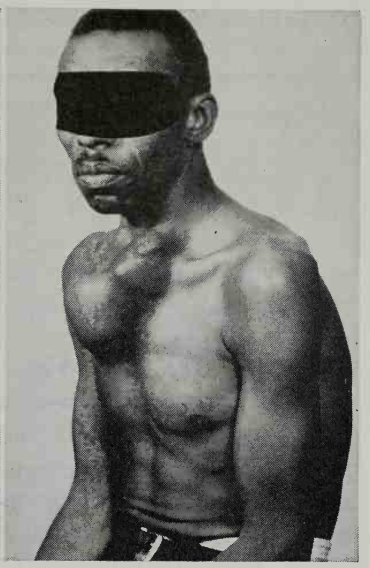


Fig. 18

Figure 17. Aneurysm of the ascending portion of the aortic arch.
Figure 18. Aneurysm of the ascending arch with erosion of clavicle and ribs.

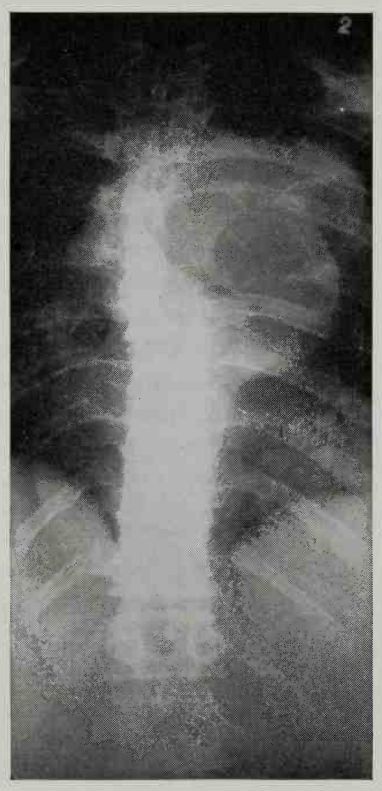


Figure 19. Erosion of spine and ribs by aneurysm of the descending aortic arch. (Kampmeier: Essentials of Syphilology.[6] Courtesy J. B. Lippincott Co.)

Table 5. *Syphilitic Aneurysms of the Abdominal Aorta: Distribution as to Age, Sex and Color*[23]

AGE IN YEARS	NEGRO MALES	WHITE MALES	NEGRO FEMALES	WHITE FEMALES
20 to 24	3	—	3	—
25 to 34	8	5	3	—
35 to 44	20	2	2	—
45 to 54	9	3	—	1
55 to 64	4	1	—	2
65 and up	1	—	—	—
No age given	1	—	—	—
TOTAL	46	11	8	3

physician it should be pointed out that in the differential diagnosis of mediastinal disease, with involvement of one or more anatomic structures, saccular aneurysm must be included along with other space-occupying lesions. Pulsation found at fluoroscopy, if not on physical examination, usually is diagnostic; in an occasional instance a firm laminated clot may prevent pulsation. I have knowledge of good surgeons exploring the mediastinum expecting to attack a solid tumor, and encountering an aneurysmal sac which, upon manipulation resulted in sudden rupture and death. This merely points up the uncertainty of an absolute diagnosis.

Today the frequency of arteriosclerotic aneurysms of the abdominal aorta and the lessened number of syphilitic ones has led some authors to declare that syphilitic aneurysms of the abdominal aorta do not occur. The thoughtful clinician will not make such an assumption, particularly if he will recall the anatomic site of the syphilitic aneurysm as above the level of the renal artery, and the arteriosclerotic one usually below this level. He also should consider the patient's age. Arteriosclerotic aneurysm of the abdominal aorta occurs in an older age group, the syphilitic one in a younger group. This is emphasized in the accompanying table (Table 5). The present-day confusion on this topic has arisen because of the decreasing frequency of the late lesions of syphilis and an increase in the aged population. Furthermore, the refinements of surgery have stimulated accurate diagnosis of arteriosclerotic aneurysms of the abdominal aorta for their surgical removal.

Serologic Findings

It is important to emphasize that a fair percentage of patients who are ill and are dying of syphilitic aortic insufficiency have negative serologic tests, whether of the flocculation or complement fixation variety. Rosahn[3] found in his autopsy studies on 380 syphilitics, that 197 had positive serologic tests, and 116 negative tests at the time of the last hospital admission. He found that about one-fourth of all syphilitics with specific anatomic lesions had negative blood tests on the last admission to the

hospital. Of those who died primarily as the result of syphilis, about 80 per cent had positive tests. This is in contrast to an incidence of anatomic changes of syphilis in only about one-sixth of those who had had serologic reversals. In our study of 163 cases of syphilitic aortic insufficiency, 139 had positive serologic tests; in 23 cases the tests were negative, but in 19 of these there was collateral evidence of syphilis. Figures from several sets of statistics indicate that from 10 to 15 per cent of patients with syphilitic aortic insufficiency will be negative to the usual nonspecific or screening serologic tests. It is possible that the incidence might be different with the more consistent results of the VDRL tests, but there are no recent statistical studies in this respect. However, I do know that the VDRL test may be negative in the presence of syphilitic aortic insufficiency, and in several of such instances a positive result was obtained with newer antigen-antibody reactions, as with the fluorescent antibody technique, for example.

The possibility of negative serologic tests accompanying an aneurysm is the same as that of aortic insufficiency and needs no further comment.

Treatment

As one leaves the possibility of certain biologic cure in the treatment of acute or infectious syphilis, one enters an area of uncertainty and difficulty in evaluation of the effectiveness of treatment of the presumably late latent syphilitic who unquestionably has focal disease, whether of proliferative or gummatous type. That inflammation and healing with scar occurs in aortitis is without question. What the factors are which permit the focal activity of the gumma is unknown. It is probably difficult of proof that treatment in the late latent stage alters the eventual outcome of syphilitic disease in the patient. It is even conceivable that in the case of the aorta a therapeutic paradox might hasten morbidity by the resolution of inflammation and consequent healing with deforming scar. This is seen dramatically upon occasion—the development of rapidly progressing aortic regurgitation under treatment. On the other hand, if one refers to the incidence of late syphilis as shown in Figure 3, the figures may reflect the effect of intensive treatment (in pre-penicillin days) of many patients with late latent syphilis who were brought under treatment through case finding. Thus, it may be permissible to draw the conclusion that treatment in late latency is effective!

Rosahn,[3] however, in analyzing his autopsy material in the light of treatment, is not sure how much is gained by treatment. Anatomic lesions of syphilis were found in 77 or 38.9 per cent of untreated patients, and he points out that only 23.2 per cent of the whole group died primarily as the result of syphilis. (See also paper by Clark and Danbolt in this issue.) He arrives at the conclusion that in treated syphilis the case fatality rate is about 1 in 5, and indicates that treatment could not have altered the course of the disease in more than four out of ten patients, since six out of ten died with no evidence of syphilis at autopsy. Actually three out of ten

with syphilis died of unrelated disease, and he speculates that treatment might have affected only two of ten who actually died of syphilis. On the other hand, these figures cannot be accepted without thinking in qualifying terms of today's population. With the better control of infectious diseases, particularly pneumonia and tuberculosis, and advances in surgery which permit extension of life, it would seem that the added years might permit the development of the fatal lesions of syphilis. (For example, it seems that more instances of syphilitic heart disease are recognized among the aged today than a couple of decades ago.) Furthermore, if we recognize the effectiveness of treatment in syphilis of the central nervous system, particularly paresis, where we can readily and satisfactorily measure the effect of treatment, and also recognize the satisfactory response of the gumma of skin or bone to antisyphilitic treatment, one cannot help but draw the conclusion that antisyphilitic treatment must have a similar effect upon the subclinical lesions caused by the treponeme.

Following treatment, however, it must be emphasized that the patient be kept under careful observation for some time thereafter. Just as sero- and clinical relapse may occur in the patient following the accepted method of treatment for infectious syphilis, relapse as shown at times in the spinal fluid of the treated paretic, and occasionally in recurrent gummatous inflammation indicates that the disease is not necessarily completely controlled by accepted standards of antisyphilitic treatment.

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Some Aspects of Neurosyphilis

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In the last edition of Sir Jonathan Hutchinson's book, "Syphilis," published in the early years of this century, we find the statement, "It is perhaps not too much to assert that there is scarcely a single type-form of disease of the nervous system which has not its representative in the chronicles of syphilis."[1] This sweeping assertion is justified by the chronicles of syphilis recorded in the late nineteenth and early twentieth centuries, but it must be modified today and it was probably an exaggeration in Hutchinson's time for we cannot be sure that neurosyphilis actually accounted for all the ills of the nervous system attributed to it in the early years of this century.

It is still true, however, that no single disease has been responsible for so many different pathologic reactions in the nervous system as syphilis. Hence, neurosyphilis is easily confused with other central nervous system diseases, and confirmation of the diagnosis by spinal fluid tests is usually necessary. By relying on clinical judgment alone the neurologist, who has also had much experience with syphilis, will undoubtedly be right more often than wrong in diagnosing symptomatic neurosyphilis, but the greater his experience with syphilis, the more he will rely on spinal fluid tests not only for the diagnosis but also for determining the activity of the syphilitic process.

While I was at Bellevue Hospital in New York City, patients with positive serologic tests for syphilis were sometimes referred to the syphilis service for fever therapy because of presumed active neurosyphilis, in spite of negative spinal fluid tests for syphilis, i.e., negative complement fixation or flocculation tests and normal cell counts. The late Dr. Bernard Dattner, an able neurologist, who was in charge of the neurosyphilis cases at Bellevue Hospital, was convinced, from his long experience with syphilis in Vienna and New York, that active neurosyphilis could not be diagnosed in patients who had negative complement fixation tests for syphilis of the spinal fluid and normal cell counts.[2] Before I knew Dattner, I was con-

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vinced that I had never seen active neurosyphilis in patients with negative complement fixation and flocculation tests for syphilis of the spinal fluid, but I was by no means certain that the activity of syphilitic processes in the central nervous system could be determined by cell counts. This was a revolutionary idea in 1937 when Dattner began his work at Bellevue Hospital. I was convinced of its validity only after several years of careful observations of patients treated for neurosyphilis by fever therapy. The first essential in such observations was to make sure that spinal fluid cell counts were made as accurately as possible. A technician was specially trained for this purpose and great pains were taken to prevent contamination of the spinal fluid with red cells when the fluid was collected.

By the late 1940's Dattner's ideas had become more or less accepted by most physicians working with neurosyphilis in this country, but reports of exceptions to the rule were not uncommon. In my own experience, exceptions to this rule were very rare and uncertain, but, in a disease like syphilis, to claim that exceptions never occurred would be much too dogmatic. Exceptions may well have occurred, but unfortunately it was usually impossible to prove or disprove them because of the subjective factors in evaluating clinical symptoms and the frequent inaccuracy of spinal fluid cell counts. The most that Dattner or I could say in such cases was that in our experience we seldom, if ever, had satisfactory proof that active neurosyphilis could exist with normal cell counts of the spinal fluid. To test our belief we gave fever therapy or penicillin to patients suspected of having active neurosyphilis, in spite of normal cell counts and (in some cases) negative specific tests for syphilis of the spinal fluid, but we were never satisfied that these patients benefited from such treatment. Neither we nor those who disagreed with us were free from charges of bias, but it seemed to Dattner, whose competence as a neurologist was seldom challenged, that there was far less opportunity for biased judgment in neurosyphilis when reliance was placed on spinal fluid tests than on clinical judgments, provided the laboratory tests were made accurately. Failure to diagnose some other disease of the central nervous system in a patient known to have syphilis does not necessarily prove neurosyphilis.

Consequently the early chronicles of neurosyphilis, written before spinal fluid tests were known, are inevitably open to question. But, despite justifiable skepticism, the early case histories of neurosyphilis cannot be rejected out of hand merely because they don't fit contemporary ideas or our own experience. Syphilis may have altered more than we realize in the course of the past century. Hutchinson, who knew nothing about spinal fluid examinations for syphilis, attributed to neurosyphilis a great array of disorders of the peripheral nerves and central nervous system. In his book we read of headaches, cranial nerve palsies, multiple neuritis of peripheral nerves, paraplegias and paralyses, including hemiplegias, occurring often in syphilis of from nine months to a few years' duration.[3] We would like to know which of these phenomena were caused by early syphilis and

which by late syphilis, if indeed they were all syphilitic. Hutchinson does not help us answer this question because he was vague about the differences between early and late neurosyphilis, even though he was well aware of the differences between primary, secondary and tertiary lesions of the skin, mucous membranes, bones and organs like the liver. His tertiary lesions were chiefly gummas or gummatous reactions which must be differentiated from the inflammations and atrophies of neurosyphilis which start early in the late stage or not at all and progress very slowly.

Except for the acute meningitis of secondary syphilis, many of Hutchinson's cases of relatively early neurosyphilis, if correctly diagnosed, represent a more virulent form of meningovascular syphilis than has been reported in more modern textbooks. Probably some of his "spinal paralyses" and hemiplegias were actually gummatous reactions involving blood vessels and other central nervous system structures. When he tells us that the signs and symptoms he describes responded well to mercury therapy, we cannot make light of his diagnoses. But therapeutic tests are not always reliable proof of diagnoses. For example, we can find in the literature on syphilis many contradictory opinions about the effect of heavy metal therapy in such phenomena as tabes dorsalis, general paresis and interstitial keratitis. Hutchinson thought that syphilis predisposed to tabes and paresis but did not cause them, yet, somewhat paradoxically, he advised mercury for general paresis and maintained that some paretics had immediate benefit from it.[4] We know today that interstitial keratitis and eighth nerve deafness associated with congenital syphilis respond well only to corticosteroids, yet prior to the advent of the corticosteroids, there were many conflicting opinions about the value of treponemacidal agents in these conditions.

However skeptical one may be of the early chronicles of syphilis, I think that there can be no doubt that the acute lesions of secondary syphilis and the early manifestations of the late stage have become much less virulent with the passage of time and this may be especially true of neurosyphilis. I think that Dr. Kampmeier, whose many years of service in the diagnosis, treatment and control of syphilis we are honoring, will agree that the acute meningitis of secondary syphilis has become much less severe within his own experience. I am quite certain that it has in mine. Unless my memory (without access to old records) misleads me, I saw more cases of secondary syphilis with the classical signs of meningitis—headache, stiff neck, positive Kernig's sign and palsy of one or more cranial nerves—in the 30's than in the 40's when early syphilis was at its peak. Since the 40's I have neither seen nor heard of a syphilitic meningitis with such pronounced symptoms.

Whether the late manifestations of neurosyphilis such as primary optic atrophy, tabes dorsalis and general paresis would be found in smaller percentages of uncured syphilitics now than in the early years of this century is impossible to prove one way or the other because penicillin

prevents late symptomatic neurosyphilis, as was impossible in the majority of clinic patients during the years when prolonged treatment with heavy metals was used. So many of the patients treated for late symptomatic neurosyphilis at Bellevue Hospital gave histories of previous irregular and inadequate treatment with heavy metals[5] that I sometimes wondered if irregular treatment with small doses of arsenicals, such as 0.3 gm. of neoarsphenamine, was not more provocative of symptomatic neurosyphilis than suppressive or preventive. Fortunately the opposite of this speculation seems to be true of penicillin. Apparently even noncurative doses of penicillin are helpful in suppressing or delaying the progress of neurosyphilis. Otherwise I think more cases of late symptomatic neurosyphilis would be encountered than we have evidence of.

Rates of first admissions to mental hospitals in the United States because of general paresis fell from 6 or slightly over in the 1940's to 0.4 in 1960, the last year for which I have data.[6] The rates may have declined still further since 1960, but, with the increased incidence of early infections since 1957, we cannot be sure about the future of general paresis. If paretics should increase in the future, it will be a sad commentary on our case-finding methods because we usually have from 10 to 20 years to find and treat the syphilis before mental symptoms develop.

SPINAL FLUID TESTS FOR SYPHILIS

Their Function

Prior to the advent of penicillin, the prevention of symptomatic neurosyphilis depended largely on spinal fluid examinations made before the onset of symptoms. Fortunately for the patients, this is no longer true because asymptomatic neurosyphilis can now be cured, as a rule, by dosages of penicillin that are used for late latent cases. No doubt the perfectionist would always like to know if asymptomatic neurosyphilis is present, but unless one is prepared to do follow-up spinal fluid examinations every six months for at least two years after treatment of asymptomatic neurosyphilis, one will have not only fallen short of the perfectionist goal but also have failed to benefit the patient in any way. Therefore, unless one is engaged in a research project and is prepared to take personal responsibility for spinal fluid cell counts, I think routine spinal fluid examinations of late asymptomatic syphilitics should be discouraged. Even when asymptomatic neurosyphilis is present, the risk of progression to symptoms after a patient has received 4.8 million units of repository penicillin[7] is so slight that in my opinion it does not justify the inconvenience to the patient of lumbar taps every six months for at least two years.

But, as previously mentioned, spinal fluid examinations are of crucial importance in differentiating symptomatic neurosyphilis from other diseases

of the central nervous system. For this reason, at the risk of boring those who are familiar with the tests, some detailed information about the tests must be given for those who have had little experience with them.

Types

Specific Tests. Biologic false positive tests for syphilis of the spinal fluid with lipid antigens are rarely, if ever, encountered. Consequently, positive conventional tests for syphilitic reagin in the spinal fluid are reliable evidence of past or present neurosyphilis. Following successful treatment of neurosyphilis, quantitative positive specific tests usually decline gradually but, as a rule, remain positive for some years.

Cell Counts. When associated with positive spinal fluid specific tests for syphilis, increased cell counts of more than 4 per cu. mm. indicate an active syphilitic process in the central nervous system. Following treatment of active cases, the cell counts should become normal within six months. Relapses are indicated by a renewed pleocytosis. Lymphocytes, plasma cells and other mononuclear cells will usually remain intact for 24 hours in sterile spinal fluid kept in an icebox, but, since the cells disintegrate quite rapidly at room temperatures, the sooner cell counts are made after the fluid is drawn, the better. Before making counts, the fluid should always be well shaken to dislodge cells from the sides of the tube or container. Red cells inevitably interfere with counts of lymphocytes in the spinal fluid when one is concerned with low counts of 4 or more per cu. mm. Therefore, every effort should be made to avoid contamination of the fluid with red cells when the fluid is drawn.

Total Protein Tests. The normal range of total protein in the spinal fluid, as determined by the tests usually used, is from 20 to 40 mg. per 100 ml. Individuals differ in the quantities that are normal for them. Active neurosyphilis is frequently associated with increased total protein but abnormally high values may persist for from one to two years after successful treatment for neurosyphilis.

Colloidal Gold Tests. These tests are not a reliable guide to the activity of neurosyphilis. First zone curves indicate parenchymatous damage. They are usually found in cases of general paresis and multiple sclerosis. Abnormal curves usually persist for at least several years after successful treatment of neurosyphilis and they are not influenced by retreatment.

TREATMENT OF NEUROSYPHILIS

Penicillin is the treatment of choice for all types of neurosyphilis. According to the reports of Hahn and co-authors on the results of treatment of asymptomatic neurosyphilis[8] and general paresis[9] in 12 co-operating medical centers, 6 million units of repository penicillin are probably ample for general paresis as well as asymptomatic neurosyphilis. This treatment

is preferably given by injections of 1.2 million units of procaine penicillin in oil and aluminum monostearate (PAM) every three or four days for five injections.

It would be of value to know the minimal effective dose of penicillin for neurosyphilis but there is little or no likelihood that this can be determined in the near future. I suspect that a single treatment with 2.4 million units of benzathine penicillin would provide ample treatment for most cases. There is no reason, so far as I can determine, why neurosyphilis should require more treatment or larger doses of penicillin than secondary syphilis, but I have no data to confirm this suspicion and unless one can obtain a two-year follow-up with spinal fluid examinations on a representative series of cases, there is no point in trying minimal doses.

Treatment with penicillin unquestionably causes healing of the syphilitic processes in the central nervous system, but healing of late lesions occurs with scar tissue and it is impossible to restore normal function when irreparable damage has occurred to important tissues. Patients treated for general paresis may improve dramatically after penicillin, but they do not have the same powers of concentration as before the paresis developed and some require custodial care for the rest of their lives. In our experience at Bellevue Hospital, if paretics failed to improve promptly following treatment with penicillin, further treatment with higher dosages was ineffective.[10]

In penicillin-sensitive cases, erythromycin is now advised as the most effective and practical substitute for penicillin. Based on experience in the treatment of early syphilis,[11] erythromycin given orally in 500 mg. doses four times a day at four or five-hour intervals for 10 to 15 days should be ample treatment for all forms of neurosyphilis. General paresis was treated successfully at Mayo Clinic with 750 mg. of chlortetracycline four times a day for 15 days, but few patients will tolerate such prolonged treatment with high doses of this antibiotic without gastrointestinal symptoms.[12]

CONCLUSION

Although all types of neurosyphilis can now be completely arrested or cured with penicillin, the goal we need to keep in mind is the prevention of symptomatic cases. This goal is on the way toward attainment and it should be attained in the near future, if all medical facilities are alert in discovering syphilis before late symptoms develop.

Much of the glamor formerly associated with the diagnosis and treatment of neurosyphilis is now gone and, in preparing this paper, I have been conscious chiefly of reminiscing. There have been moments when I have been tempted to relegate neurosyphilis to the limbo of medical history, but, lest we yield to this temptation, it is well to remember that our ignorance of the underlying mechanisms responsible for the hypersensitive reactions

observed in neurosyphilis is profound. Obviously the *T. pallidum* is a sophisticated organism which learned long ago to take advantage of weaknesses and errors in the long evolution of immune mechanisms in man. How little we understand these immune mechanisms is shown by our failure to explain them in neurosyphilis. It is notable that modern textbooks on immunology avoid discussing syphilis apart from the laboratory tests used as aids to diagnosis. Yet no other single disease presents so great a challenge to immunology. How the body decreases demonstrable treponemes to such small numbers in all late lesions except the meningoencephalitis of general paresis is still unknown. Nor do we know why some central nervous system tissues react with inflammations and others only with degenerative lesions. These are important questions for immunology and until we are able to answer them we can ill afford to forget neurosyphilis.

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Prenatal Syphilis

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The incidence of prenatal syphilis has continued to decline over the past 20 years. There were 4085 cases of prenatal syphilis reported in 1962, of which the great majority were in adults who were born with the disease. Only 330 members of this group were children of one year of age or less. This, however, is very alarming because there has been a gradual increase in prenatal syphilis in this age group since 1957. The 1962 total for children under one year of age represents a 100 per cent-plus increase over the 1957 total for the same group. Attention should be drawn to these patients, because prenatal syphilis, an entirely preventable disease, should not occur with proper prenatal care.

Prenatal syphilis is syphilis transmitted to the fetus in utero by the mother. The infection occurs through the placenta, and it seldom, if ever, takes place before the fourth month of gestation. Spirochetes are not found in fetal tissue prior to 18 weeks of intrauterine life. It has been suggested, and we concur, that a barrier to the passage of the *Treponema pallidum* is created by the well developed Langhans layer of the chorion.[6] After the sixteenth week, this layer is not found in the placenta, and fetal infection may ensue. Thus, adequate treatment of the pregnant mother prior to the fourth lunar month of her pregnancy will prevent congenital infection. Adequate treatment of the mother after 18 weeks of gestation will bring about a cure in utero if infection has occurred; however, treatment cannot prevent possible osseous stigmata. Also, one cannot predict the later occurrence of Clutton's joints, neural deafness, or interstitial keratitis following adequate antiluetic treatment. It is of interest that the *Treponema pallidum* has not been identified in these lesions by most workers, and thus they may represent phenomena of hypersensitivity.

Spirochetemia may result in fetal wastage or neonatal death. Thomas[4] states that 25 per cent of fetuses infected in utero in untreated cases die

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before birth. Another 25 to 30 per cent will die shortly after birth if untreated. Of all those infected, untreated children who survive infancy, 40 per cent develop late symptomatic syphilis.

With regard to twins, identical (single ovum) twins are both infected or neither one is infected. However, with nonidentical (double ova) twins, infection of one and not the other has been reported.[3] This is easily explained by the presence of two placentas, one for each child.

Another interesting phenomenon is the event of third generation syphilis. Although several cases have been reported and appear to be authentic, the authors are hesitant to accept such an occurrence. Third generation syphilis may perhaps exist, but more likely it represents maternal reinfection. Dr. Udo Wile has a photograph of a young Negro woman with a chancre on her lower lip and classical Hutchinsonian upper central incisors.

CLINICAL MANIFESTATIONS

The clinical manifestations of prenatal syphilis include early lesions, late lesions, and stigmata which are the results of scarring.

Early Manifestations (Figs. 1–6)

Active signs and symptoms at birth denote a serious prognosis. Usually the infant appears well at birth, and the early lesions are not observed until the second to sixth week postpartum. Occasionally, a year or two may pass before the early signs are manifest. The early clinical lesions are those of secondary syphilis; however, they are more severe than the acquired secondary lesions in the adult. In general appearance the infant usually has a well-formed body that may be slightly underweight. The "classic" picture of marasmus, pot belly, withered skin, old man facies and pseudoparalysis of Parrot is most often seen in premature infants and associated with severe infection.

The early *cutaneous lesions* resemble those of acquired secondary lesions. Their distribution is a significant feature, and involvement includes the circumoral region, palms, soles and anogenital area. Vesicular or bullous involvement of the palms and/or soles is somewhat uncommon, but highly diagnostic. Annular lesions may be striking; however, ulcerative lesions are rare. Kampmeier noted cutaneous lesions in 52 per cent of patients under the age of six months.[1] Darkfield examinations are usually positive.

More common than skin eruptions are *lesions of the mucous membranes and mucocutaneous areas.* Rhinitis causing snuffles is a common finding and often is the first clinical manifestation of prenatal syphilis. The nasal discharge may be hemorrhagic, and it is always very infectious. In addition to involvement of the mouth, throat and nose, fissures may occur about the lips or perianally. The scarring which results from healing forms

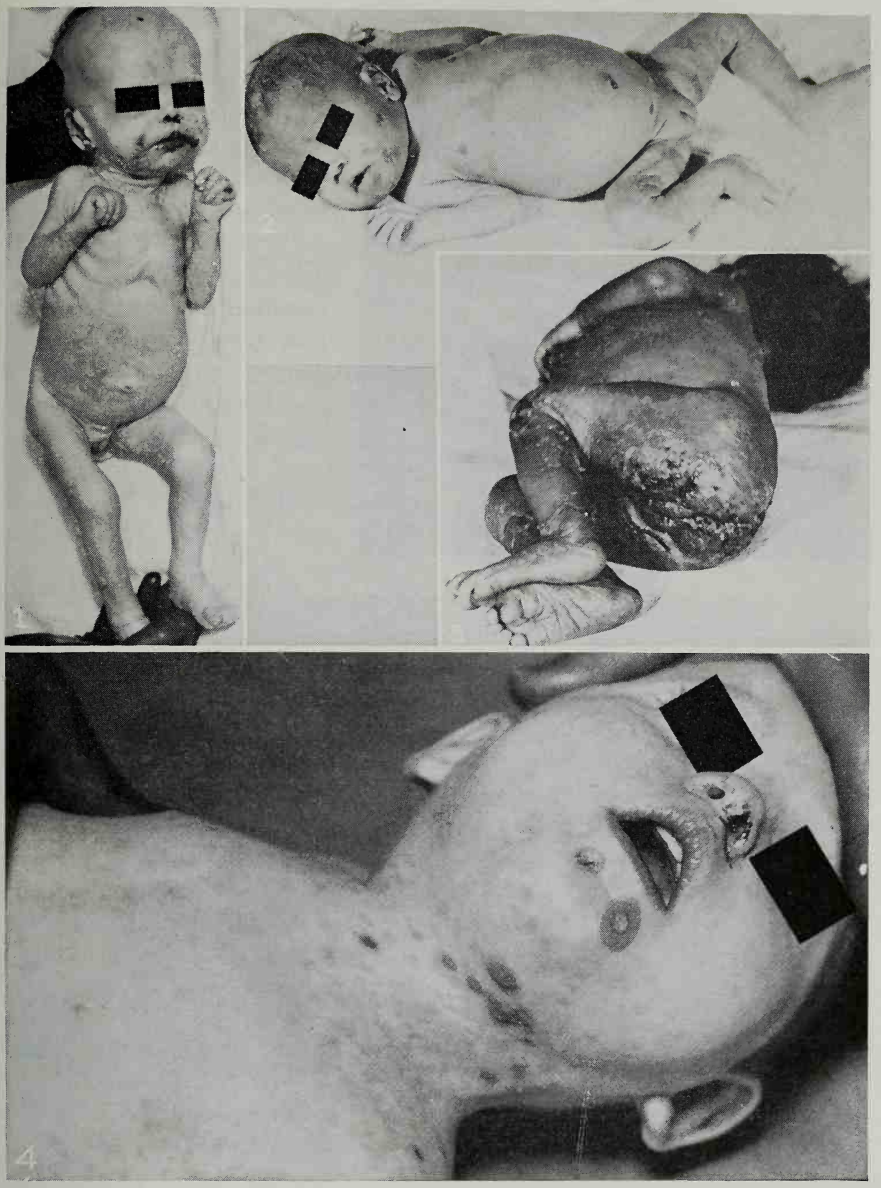

Figure 1. Marasmic infant showing snuffles and perioral lesions.*

Figure 2. Syphilitic infant with "pot belly" and annular cutaneous lesions. These children often have a hepatosplenomegaly.

Figure 3. Cutaneous manifestations of prenatal syphilis involving perineal area.

Figure 4. Papulosquamous eruption of prenatal syphilis with snuffles. Note the annular characteristics of some lesions.

* Figures 1 through 7 by courtesy the Department of Pediatrics, Vanderbilt University School of Medicine.

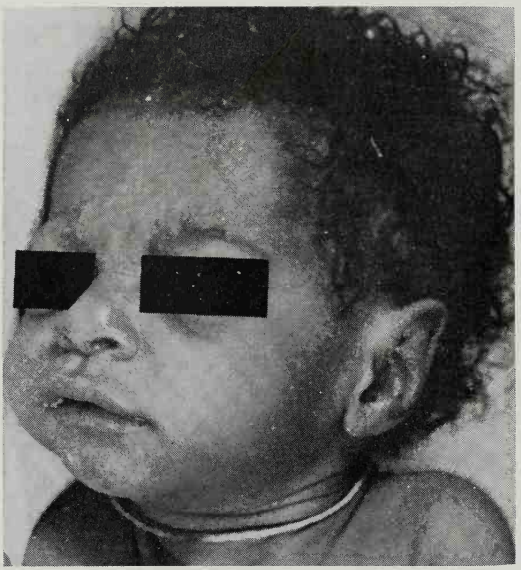

Figure 5. Syphilitic bullous eruption of face, with annular lesions of forehead and split papules at corners of mouth.

Figure 6. Cutaneous lesions of face secondary to snuffles. Note rupial lesions on hand.

rhagades. In addition to these lesions, condylomata lata are occasionally observed.

While snuffles is an early clinical finding, the *most* common early manifestations involve the *bones and joints.* The long bones are usually involved, and the most common lesion is osteochondritis. Characteristic of this lesion is the "saw-tooth" metaphysis seen in the roentgenogram. The intense pain and tenderness of osteochondritis underlie the pseudoparalysis of Parrot. An associated feature is periostitis which is also painful when

acute. In later life this can account for blunting of the scapular spines and anterior tibeal margins. Rarely a form of osteitis of the phalanges can lead to syphilitic dactylitis, which is seen during the first two years of life. Usually the radiological changes of osteochondritis seen in the ends of the long bones are gone by the eighth month. However, periostitis can be observed during the entire last half of the first year of life.

Hepatosplenomegaly is a frequent finding clinically. Kampmeier[1] noted a 64 per cent incidence, which was the most frequent clinical finding in his group of cases. Reports of jaundice and edema secondary to hepatic involvement are recorded.

Meningitis occurs in 40 to 50 per cent of babies born with prenatal syphilis. The involvement may be asymptomatic, and the diagnosis is dependent upon spinal fluid examination.

Other findings associated with early syphilis include: anemia, saddle nose, pneumonia alba, generalized lymphadenopathy, peritonitis, nephrotic syndrome,[7] iritis, and choroiditis. (Chorioretinitis is a late manifestation in prenatal lues.)

Late Disease (Figs. 7, 8)

The late lesions of prenatal syphilis correspond to the tertiary lesions of acquired syphilis. Generally, the lesions develop after two years of age, and seldom occur past the age of 30 years.

Interstitial keratitis occurs in 30 to 50 per cent of cases. It may rarely be seen in acquired syphilis.[3] The lesion consists of vascularization of the cornea with precipitation of cells and pigment on the posterior surface of the cornea. The lesion is more common in females, and frequently is seen during the early teens. Ulceration is rare, and the process is usually accompanied by photophobia. The majority of episodes involve both eyes, although the phenomena may present initially in just one eye. Untreated,

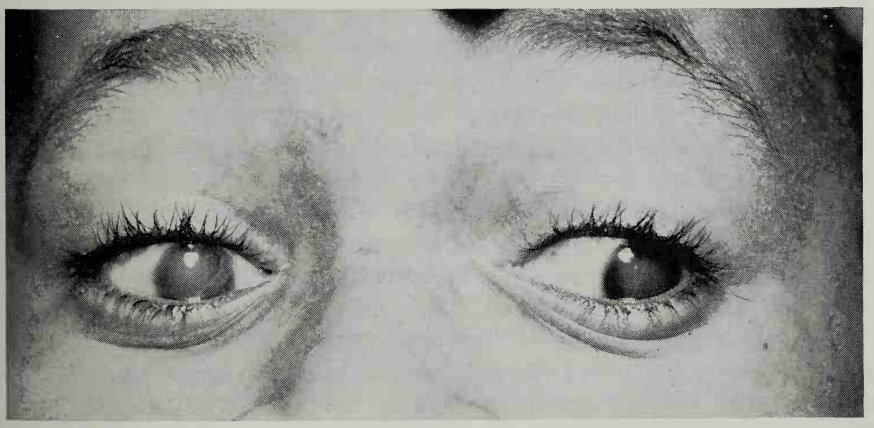

Figure 7. Interstitial keratitis due to prenatal syphilis. (Kampmeier: Physical Examination in Health and Disease. Courtesy F. A. Davis Co.)

Figure 8. Clutton's joints.

a course of 12 to 18 months may be expected. The lesions do not respond to antiluetic treatment. The treatment of choice is topical steroids. Ashworth[8] reports on the five-year follow-up of 50 cases, and states that the treatment is effective. The expectation of visual acuity after treatment is good. There is little or no corneal scarring, and the presence of corneal vascularization in early cases had no ill effect on the good prognosis. It is interesting that Putkonen[9] found no interstitial keratitis in his 36 patients who received adequate early antisyphilitic treatment. In the event of inadequate treatment and late leukomatous scarring of the cornea, corneal transplantation can be utilized to restore vision. Owens'[10] series showed that approximately half of the grafts remained clear. Other eye lesions are seen occasionally with interstitial keratitis, and these include iritis and iridocyclitis early and glaucoma late.

Neurosyphilis is probably the second most common lesion of late congenital syphilis. The diagnosis depends upon spinal fluid examination. The diagnosis is usually established during the teens, but may be seen after the fifth year of life. As is true in the acquired forms also, the lesion is more common in the white race. The overall incidence in the white race is approximately 12 per cent, as compared to approximately 3 per cent in Negroes. The various clinical manifestations of acquired neurosyphilis are seen in children but there is seldom sharply defined tabes or paresis. Less than 1 per cent will develop paresis. The poor prognosis of neural syphilis prior to penicillin treatment is no longer tenable. The prognosis with adequate treatment is very good.

A very late manifestation of prenatal syphilis is the uncommon occurrence of *neural deafness*. Generally, neural deafness is accompanied by a normal spinal fluid examination. The prognosis in untreated cases is poor. Even with antiluetic treatment, the deafness is relentlessly progressive. The deafness usually does not develop before adult life, and it may be

associated with findings of dizziness, vertigo and tinnitus. Hahn, Rodin and Haskins[11] have recently reported the use of steroids in the treatment of neural deafness with good results. They found improvement in 10 of 19 patients with treatment. Usually patients are better within two weeks; however, the authors recommended a month's trial of therapy. Morton[12] has shown that radiological study of the petrous temporal bone in this disorder is negative.

The development of *gummas* and *gummatous inflammations* in congenital lues is similar to that of acquired syphilis.

Clutton[13] described *bilateral hydrarthrosis* (Clutton's joints) in 1886. This is a syphilitic synovitis without involvement of bone or cartilage. It affects the knees most commonly, and is usually bilateral. It occurs generally between the ages of 8 and 15 years. It begins acutely or subacutely, and resolves spontaneously without residual joint damage within several months. The clinical picture includes fever, and contrary to Clutton's original description, the joints may be red, warm and painful. The lesions respond to steroids, but not to penicillin or salicylates. Borella, Goodbar and Clark[4] have described eight cases recently, and point out the need for accurate diagnosis so that harmful treatment will not be given. As indicated by them, the major diseases to be ruled out include pyogenic arthritis, Still's disease, sickle disease, lupus erythematosus and acute rheumatic fever.

The association of *arthritis* with congenital syphilis has been reviewed by Gray and Philp.[15] They point out that arthritis occurs in two forms with congenital syphilis, and a third form common to both congenital syphilis and acquired syphilis. Osteochondritis appears in infants, while Clutton's joints are the more common manifestation in older children. The third form is similar to the arthritis of acquired tertiary syphilis of adults. This form may be synovial or osseous. The synovial form is seen in children and is actually a perisynovitis. The osseous form begins as an epiphysitis and eventually involves all the structures of the joint. This chondro-osteoarthritis is the rare von Gies joint, and may lead to ankylosis. Radiologically, involvement of the articular cartilage may be recognized by diminution in the joint space. Bone erosion may appear within the involved joint, and is seen centrally. The marginal types of erosion seen with tuberculosis have not been described in congenital syphilitic arthritis.[15] The earlier the diagnosis and treatment, the better is the prognosis.

It is of interest to note that the juxta-articular nodules which rarely occur in acquired syphilis apparently do not occur at all in prenatal syphilis.

It was once the feeling that prenatal lues tended to spare the *cardiovascular system.* More recently, however, there have been many reports which make such an observation doubtful. Bonugli[16] has described a series of 15 cases in which there is good evidence that patients with prenatal syphilis do develop aortic and aortic valvular lesions. The involvement occurs at various ages, but is extremely rare.

Stigmata (Figs. 9–13)

Some of the lesions of prenatal lues produce scars which persist as stigmata of the disease. Many of these findings occur on or about the face. The *saddle nose* resulting from rhinitis and/or destructive osseous changes is one of them. Also significant is the *nasal septal perforation* occasionally encountered. Luetic involvement of the skull in infancy may produce bony overgrowth and the resultant *frontal bosses*. The maxilla and mandible may be similarly involved. The destructive cutaneous lesions about the lips and cheeks may scar, to produce *rhagades*. While not so obvious, another stigma is the lesion of *choroiditis*.

The most pathognomonic sign of prenatal lues is the presence of *Hutchinsonian upper central incisors*. Putkonen[17] found an incidence of 44.7 per cent in his series of 254 patients with prenatal syphilis. He stresses the importance of the shape of these permanent teeth. They are barrel-shaped or show a convergence of both lateral margins toward the cutting edge. The crescentic notch of the cutting edge is only of diagnostic value when covered by enamel. Syphilitic involvement of the first molar, so-called bud molar or Moon molar, was present in 22 per cent of these cases. Putkonen and Paatero[18] have also demonstrated that x-ray study of the unerupted central incisors, after one year of age, can reliably detect Hutchinsonian formation. Such examination is not reliable for first molars. One of the most interesting recent findings regarding syphilitic dental changes is their prevention by early treatment. Putkonen[9] has presented 51 cases of prenatal syphilis adequately treated during the latter half of pregnancy or during the first three months of life. In none of these patients did dental changes due to syphilis occur. Such changes did occur, however, in 7 of 15 cases treated during the fourth month of neonatal life or later.

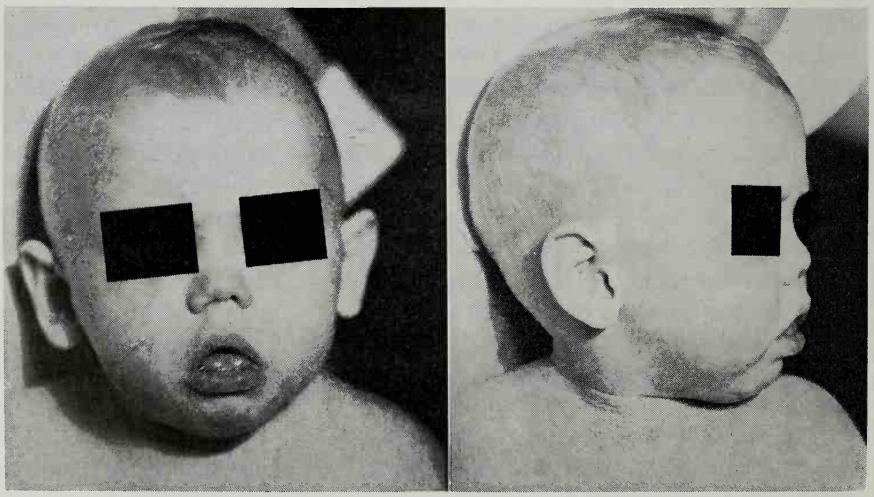

Figure 9. Characteristic syphilitic facies with involvement of the supporting tissues of the nose with mouth breathing.

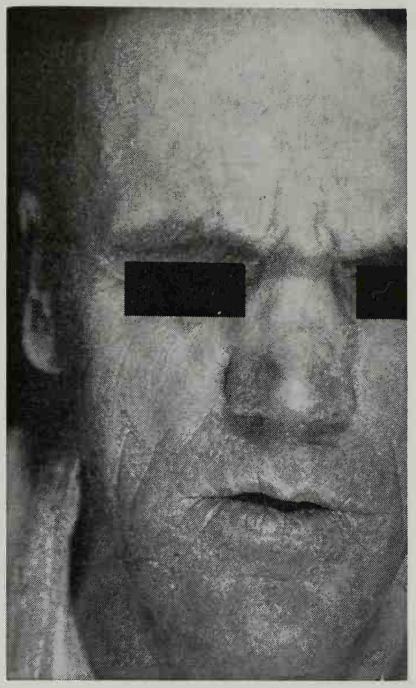

Figure 10. Syphilitic facies in an adult showing prominent frontal bossae, nasal involvement, rhagades and prognathous chin.

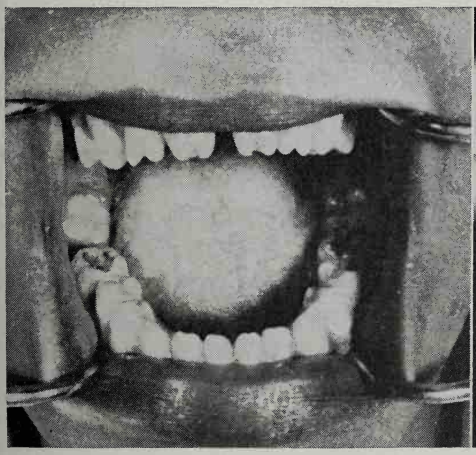

Fig. 11

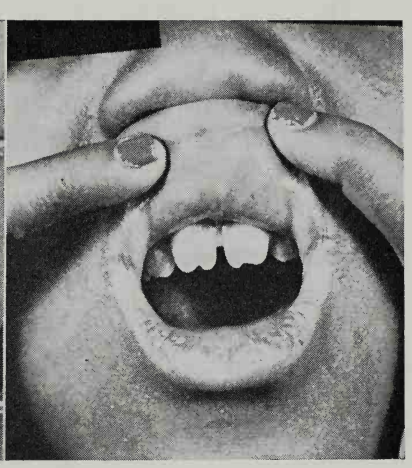

Fig. 12

Figure 11. Syphilitic dental changes of incisors and involvement of the first molars.

Figure 12. Hutchinsonian upper central incisors.

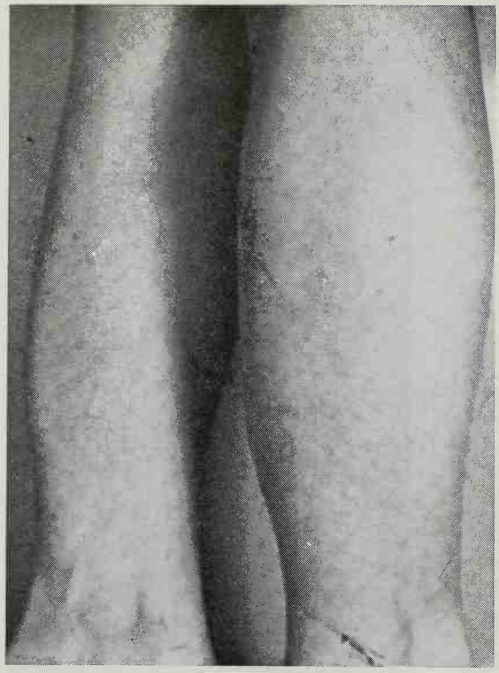

Figure 13. Saber shins.

It was also suggested that such early treatment protects against interstitial keratitis.

The classic *Hutchinson's triad* of interstitial keratitis, neural deafness, and upper central incisor involvement is actually quite rare.

The development of *saber-shin* appears after previous tibial osteitis. Another bone which is located near the surface, the clavicle, also acts as a diagnostic landmark. Unilateral thickening of the inner third of the clavicle constitutes the uncommon *sign of Higoumenakis.* A lesser diagnostic aid is the presence of a *Graves' scaphoid scapula.*

Autoimmune Phenomenon

An interesting phenomenon, not necessarily associated with prenatal syphilis, is *paroxysmal cold hemoglobinuria* (PCH). The clinical signs include muscular cramping, headache, hyperpyrexia and hemoglobinuria, which usually clears within 24 hours. Urticaria and acrocyanosis may also be present, as well as transient splenomegaly and jaundice. The typical onset is precipitated by exposure to cold and occurs within minutes or several hours. The paroxysms are reportedly decreased or possibly eliminated by adequate antiluetic treatment. A study of two interesting cases has recently been presented in the literature by Weintraub et al.[19] This work describes the Donath-Landsteiner antibody as a biphasic hemolysin of variable thermolability. In most cases the biphasic hemolysin is not inactivated by 30 minutes at a temperature of 56° C. It requires a temperature

below 15–20° C. to bring about fixation of the antibody on erythrocytes. Complement is not necessary for this fixation; however, hemolysis upon rewarming to 37° C. will not occur in the absence of complement. The optimum serum pH for Donath-Landsteiner antibodies is in the range of 7.0 to 8.0, whereas, the optimal range for cold hemagglutinins is 6.5 to 6.8. Syphilitic infection may damage or alter erythrocytes in such a way as to make them antigenic. The resultant antibody formation would thus constitute PCH as an autoimmune phenomenon. Because the erythrocyte in paroxysmal nocturnal hemoglobinuria is faulty in stromal lipids, Weintraub et al. studied the erythrocyte of PCH in this aspect. They found no such lipid abnormality in the one case examined. The Coombs' test was found to be positive in one patient studied by Parish and Mitchell.[20]

LABORATORY INVESTIGATION

A darkfield examination of the umbilical vein at delivery will be positive in more than half of the cases of congenital syphilis.

The serological examination of the patient with prenatal syphilis can be complicated by passively transferred serum factors and biologic false positivity. Over all, the cord blood obtained at delivery is of very little value because it often reflects passively transferred antibodies. It is occasionally of value if the titer is markedly greater than that of the mother. An excellent discussion of neonatal serology was presented by Rein and Reyn[21] a few years ago. The following discussion reflects their thoughts on the subject.

A seropositive pregnant woman should be investigated to determine whether she has syphilis or has a biologic false positive reaction in her serum. If one is not able to do this, the patient should be treated to protect the fetus. After birth, the child should be followed with serial quantitative serological tests for six months.

A negative serological test in a neonate does not exclude prenatal syphilis, since a fetus infected late in gestation may develop positive serological tests at variable times from birth.

The half-life of passively transferred reagin is approximately 32 days. Thus, there is a 50 per cent reduction in quantitative titers after 32 days from birth. Passively transferred reagin will not cause positive serologic tests for syphilis after three months postpartum. Passively transferred antibodies will not cause positive specific treponemal antigen tests for syphilis after six months postpartum.

The frequency and degree of seropositivity in infants depends upon several factors. The higher the mother's titer at delivery, the greater is the likelihood of neonate titer, and the longer will it be necessary to attain seronegativity. The frequency of neonatal reactors is increased by more sensitive serological tests. The type of test used is important. Passively

transferred maternal reagin in the infant's serum is more readily detected by complement fixation than by flocculation techniques. Similar titers are found in the mother and child with complement fixation tests, while flocculation tests record minimal amounts of reagin in the child's blood as compared to that of the mother. Thus, there are two antibodies: the complement fixation antibody which may pass through the placenta, and the flocculation antibody, which may not.

The levels of immobilizing antibodies are comparable in the mother and child. In the study of 30 infants by Austin and Nelson, as quoted by Rein and Reyn, the passive transfer of immobilizing antibodies was found in all instances. The time for disappearance from the serum depended upon the amount transfered. The Fluorescent Treponemal Antibody (FTA) test is positive earlier than the Treponema Pallidum Immobilization (T.P.I.) test in primary acquired syphilis; however, Vignali[22] found that in congenital syphilis both tests give the same results. Cailland and Meinicke[23] studied the results of the T.P.I. test in 19 severe cases of lues connata recens and on 12 children with passively transferred antibodies. The results were those of "classical serological reactions." The test is a useful guide to the results of early treatment. In 35 of the 36 cases treated by Putkonen,[9] the T.P.I. reverted to negative, while in the thirty-sixth case it was equivocal.

Passive transfer of antibodies causing false serologic tests and/or T.P.I. tests in children were found in 66 per cent of the cases described by Miller et al.[24]. In his series of 400 children, he found a rate of 11 per cent biologic false positives after passive transfer could be eliminated as a cause. This is lower than the rate of 40 per cent false positive sera found in adults. In addition, children do not show the preponderance of females with regard to biologic false positivity. The incidence of systemic disease in young children associated with true biologic false positivity is not high.[24]

TREATMENT

The treatment of prenatal syphilis is aqueous procaine penicillin G, 50,000 units per pound of body weight. This total dose is divided by ten and given as daily intramuscular injections.

The neonate should be followed with quantitative STS every month for six months, then every third month for one year. Ninety per cent of these cases treated adequately and early will be seronegative within one year. If the patient is two years or older when first treated, the serology may never become negative. Spinal fluid examinations should be done whenever clinical suspicion of neural syphilis is present. As a general rule, the febrile Herxheimer reaction at the start of penicillin therapy is to be expected when the clinical signs of active prenatal syphilis are present.

Prenatal syphilis can be totally prevented by frequent prenatal examinations, proper diagnosis, and adequate treatment of the infected mother.

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Worldwide Problems in the Diagnosis of Syphilis and Other Treponematoses

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The broad title given this paper makes advisable a prefatory definition of its subject matter. There is here a review of the etiology and natural history of the treponematoses. Brief consideration is also given to some of the experimental work† which has a bearing on the diagnosis of this group of diseases. Finally, some of the specific problems in diagnosis which are of importance and general interest are discussed. No effort is made to cover the literature *in extenso* and certain diagnostic problems of major importance such as biologic false positive serologic tests and the whole subject of serodiagnosis are arbitrarily omitted. The major emphasis is on the interrelation of diagnostic and public health problems.

THE TREPONEMATOSES: A REVIEW OF THE ETIOLOGY, INTERRELATIONSHIPS, NATURAL HISTORY AND EPIDEMIOLOGY

In Table 1, information regarding venereal syphilis, endemic syphilis, yaws and pinta is presented which summarizes our knowledge regarding the etiologic agent, the clinical course in man, and certain aspects of the epidemiology of each disease. In this table and elsewhere in the paper, the term "endemic syphilis" includes those manifestations of treponemal disease referred to by such words as bejel, dichuchwa and njovera in various areas of the world.

It will be noted in section 1 of the table, dealing with the etiologic agent, that while different names are ascribed to the treponemes of syphilis, yaws and bejel (pallidum, pertenue and carateum respectively), the demonstrable differences among them are limited to their behavior in animals, are quantitative rather than qualitative and are neither constant nor definitive. Given a strain of treponeme, the source of which is unknown,

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† Specific references to the experimental work mentioned in this discussion are not given. They can be located in the work of Turner and Hollander.[1]

it is impossible incontrovertibly to establish, with techniques currently available, that its origin was a case of venereal syphilis, endemic syphilis, yaws or pinta. In fact, some strains from cases of human yaws, which produce lesions in rabbits considered to be typical of yaws, have after several passages through rabbits come to produce lesions considered to be typical of venereal syphilis. The reverse trend has not been noted.

In reviewing the clinical information as shown in section 2 of the table, one is struck again by the similarities among the various manifestations of treponemal disease. They all have initial lesions followed by more extensive "secondary" manifestations and all exhibit the phenomenon of latency. The major difference is in the types of tissue involved in the late stages. Even in terms of response to therapy, the differences are quantitative. In general, it may be said that venereal syphilis is the most protean in its manifestations and that virtually any lesion produced by the other three entities may be produced by it. The spectrum of pathologic response seems to narrow as one considers in order endemic syphilis, yaws and pinta. Similarly, generalizations regarding response to therapy can be made. For example, more treatment is possibly required to effect a cure in venereal syphilis than endemic syphilis and certainly less is required for yaws than for syphilis. While the clinical response of skin lesions of pinta to treatment is apparently slower than for syphilis or yaws, the amount of treatment required to effect the response is presumably no greater than for yaws.

It is in section 3 of the table dealing with epidemiologic information that the major differences among these diseases appears. The ubiquity of venereal syphilis is striking as compared to the truly focal and limited area where pinta is found. Endemic syphilis and yaws are intermediate in this respect. These differences are paralleled by the mode of transmission: venereal syphilis largely spreads through sexual contact; the others, largely nonvenereal. The above differences apparently are determined to a great extent by the social and physical environment in which the host finds himself: the more primitive the culture, the less venereal transmission. It is believed by many that these environmental variations are the real determinants of the differences among the strains of treponemes, the manifestations in the individual human host and the human population as a whole in a given area. Certainly the variation in mode of transmission, the age distribution of the disease, the early and, possibly, even the late manifestations of the disease in the individual can be logically explained on this basis.

Before leaving this portion of the discussion, it should be pointed out that there have been many observations made during the study of experimental and naturally occurring syphilis that tend to support this view. One, the change in the types of lesions produced by strains following passage in rabbits, has already been mentioned. Another bit of evidence of great pertinence has to do with the effect of temperature. Both *in vitro* and *in vivo* experiments indicate that the optimum temperature for the treponemes is 35° to 37° C.; that as 40° C. is approached or exceeded there is

Table 1. *A Summary Presentation of Information Regarding the Etiologic Agents, Clinical Course in Man and Certain Epidemiologic Aspects of Syphilis (Venereal), Endemic Syphilis, Yaws and Pinta*

	SYPHILIS (VENEREAL)	ENDEMIC SYPHILIS	YAWS	PINTA
1. The Etiologic Agent				
a. Name	*T. pallidum*	*T. pallidum*	*T. pertenue*	*T. carateum*
b. Microscopic Characteristics				
Morphology		Indistinguishable for all		
Motility		Indistinguishable for all		
c. Antigenic Relationships (in animals)				
(1) Serologic tests		Apparent strain differences even in same species but no constant differences		
(2) Cross-immunity	Definite between species but not equal for all: syphilis tends to produce greater protection against endemic syphilis than against yaws			
d. Susceptibility to Penicillin	No significant differences *in vitro* or in laboratory animals			
e. Experimental Disease in Animals				
(1) Establishment of strain	Relatively easy	Relatively easy	Relatively easy	Extremely difficult
(2) Inoculation period (days)				
Number of strains	31	5	11	—
Minimum-maximum	14–82	53–70	28–75	—
Median	40	67	52	—
(3) Lesions (rabbits), induration and size	Generally more	Generally intermediate (Differences not constant or absolute)	Generally less	—
2. Clinical Information				
a. Incubation Period (days)				
Range	10–90	10–90	10–90	7–20
Median	21	42 (?)	21–42 (?)	(human inoculations)
b. Natural Course				
(1) Initial lesions	Usual	Occur, but commonly not noted	Usual	Occur
(2) Latency	Practically universal	Practically universal	Practically universal	Occurs
(3) Late "benign"	Not uncommon	Common	Usual	Usual
(4) Cardiovascular system	Not uncommon	Occurs	Not proved	No
(5) Central nervous system	Not uncommon	Occurs	Not proved	No
c. Serologic Findings with Wassermann or Treponemal Antigens	All positive; no definite or constant differences demonstrated			
d. Response to Antibiotics, Arsenicals and Heavy Metals	All respond but time-dose requirements for cure vary			
3. Epidemiologic Information				
a. Distribution	Worldwide	Endemic, rural, focal, less developed areas	Endemic, rural, focal, but widespread in tropical areas, primitive setting	Endemic, rural, focal, underdeveloped areas, tropical America
b. Main Reservoir (human only)	Young adults	Children (2–10 years)	Children (4–15 years)	Young persons 10–30 years)
c. Transmission				
(1) Person to person				
(a) Venereal	Common	Uncommon	Uncommon	Not described
(b) Nonvenereal	Uncommon	Common	Common	Common
(c) *In utero*	Not uncommon	Unusual	Never (some contrary opinion)[2]	Not described
(2) Indirect				
(a) Utensils, flies, etc.	Rare	Probably not uncommon	Possibly not uncommon	Not described
d. Susceptibility of Man	Universal	Universal	Presumably universal	Presumably universal
e. Period of Communicability in Man	Variable; during primary and secondary stages; (?) 2–4 years	Variable; while moist skin and mucous membrane lesions present (?) weeks to months	Variable; while moist lesions present; (?) several years	Unknown; potentially while active skin lesions present

progressive destruction of treponemes; and as the temperature falls below 30° C., multiplication ceases. These facts certainly have major implications regarding the location and nature of lesions in the individual and thus, indirectly, for the mode of transmission. Elevated temperature in a host as a result of intercurrent infection could affect the transmission of infection and the frequency of late manifestations in a population. Other factors studied which may have significance include the variation in manifestations of disease relative to the age of the host at the time of infection; the effect of the health status of the rabbit host on ease of infection; hormonal effects on manifestations of disease; site of inoculation; effect of dosage on incubation period and number of lesions; the optimal conditions provided by moisture and relative anaerobiosis; and the effect on infectiousness of lesions of "sensitization" of treponemes with the development of immunity in the host. Since, however, the purpose of this discussion is to provide a basis for considering certain problems in diagnosis and not to support or deny the unitarian concept of "treponematosis," it does not seem profitable to pursue this aspect in further detail.

DIFFERENTIATION FROM NONTREPONEMAL DISEASE

Let us now consider briefly the differentiation of treponemal from nontreponemal disease. Suffice it to say that the vast majority of cases of treponemal disease may be readily differentiated from nontreponemal disease by the application of simple history-taking techniques, physical examination, and serologic tests. Where available, darkfield examination adds a great deal to precision of diagnosis. In a small minority of cases, on a worldwide basis, the ruling out of other disease processes including biologic false positive serologic tests may test the mettle of the most skilled clinician; indeed, it may be impossible. This latter group of cases is certainly of extreme importance to the individual patient and physician. The higher the level of medical practice and the lower the prevalence of treponemal infection in a nation or community, the more importance these problems assume. Nevertheless, in terms of global problems of control or eradication and of numbers of persons involved, they currently are of far less import than certain other difficulties which will be discussed later.

DIFFERENTIATION AMONG THE TREPONEMAL DISEASES

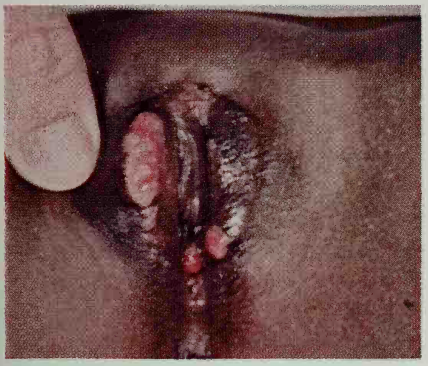
Differentiation of the treponemal diseases, one from the other, has already been touched upon. It has been pointed out that the clinical and serologic differences are largely quantitative in nature and in the individual patient it is difficult or impossible to distinguish one form from the other on these grounds alone. For example, we have seen in the Johns Hopkins

PLATE IV

A. Patient from Africa with endemic syphilis. (Courtesy C. J. Hackett, WHO, Geneva.)

B. Patient from Baltimore, Maryland, with syphilis.

A and B depict mucous patches of the lip. Both patients are males; the patient in A is a child of approximately 4 years of age; the patient in B is approximately 12 years of age.



C. Patient from Baltimore, Maryland, with syphilis.

D. Patient from Haiti with yaws.

C and D depict condylomata lata. The patient in C is a 10 year old girl; that in D, a younger child.

These illustrations show perfectly typical lesions in patients having diagnoses of syphilis, endemic syphilis or yaws. All are highly infectious, early lesions, teeming with treponemes.

Hospital a patient with signs, symptoms and laboratory evidence absolutely typical of pinta. However, the diagnosis made was that of syphilis since she had never been more than 50 miles from Baltimore in her life. Similar experiences occur in all large clinics, and venereal syphilis, endemic syphilis and yaws even more frequently present confusing similarities of expression. In areas where patients are seen who come from both "syphilis areas" and "yaws areas," this may be an interesting problem as recently discussed by Laird.[3] In terms of precision of diagnosis and personal clinical satisfaction, this is a problem of importance. In terms of successful management of the patient and protection of the public health, however, it has little significance under most circumstances. If treatment adequate for the cure of syphilis is administered, the patient is cured and the public health is protected. The coexistence of venereal syphilis in an urban area and yaws in the surrounding rural areas with varying admixtures of each have, of course, real significance for the planning of campaigns against the treponematoses. (See Plates IV and V.)

THE MAJOR PROBLEMS IN DIAGNOSIS

Today the major practical problems in diagnosis are related to such questions as: By whom is the diagnosis to be made? What diagnostic methods, if any, are to be employed? What constitutes a diagnosis? To what groups are these methods to be applied?

The question of by whom the diagnosis is to be made is a most pressing problem in most areas, although there are two aspects. The first is in those areas where there is a favorable physician-to-population ratio and a low treponemal disease rate. Here arises the paradoxical situation of more and more physicians knowing less and less about treponemal disease. As the disease rates fall, clinical material becomes less available for teaching, and the problem assumes less and less importance, not only in the mind of the public in general but among legislators, public health officials, and practitioners and teachers of medicine. There is no ready and universally applicable panacea for this. Basically the answer lies in keeping the importance of the problem before each of the groups mentioned: teachers must be encouraged to maintain an awareness of the presence and importance of the treponematoses and to take advantage of each opportunity to demonstrate clinical material both intramural and extramural as it becomes available.

The other aspect of the problem is seen in areas where the physician-to-population ratio and at times the caliber of physician is low while the prevalence of treponemal disease is high. In this situation there are two approaches. One, a long-term solution, is the development of more and better educational institutions. The other is modification of control or eradication programs so that highly trained professional persons are re-

mation regarding the effect of inadequate penicillin therapy of rabbit syphilis during the incubation period. Hollander, Turner and Nell[8] demonstrated that the incubation period was prolonged but that otherwise the evolution of the disease was apparently unaltered. Similar effects in humans would not necessarily be harmful to the patient or the community. If, however, continued or repeated subcurative treatment is given, there is some question as to whether or not the process may be masked in such a way as to allow many cases unsuspectingly to enter latency and subsequently to develop infectious relapse or late manifestations of the disease. It seems quite possible that this may indeed be the case. The disproportionate fall in reported primary and secondary syphilis as opposed to early latent syphilis in young adults noted in certain areas has been interpreted as confirmatory evidence. The possibility that subcurative treatment and consequent masking of symptoms is the cause of this discrepancy is postulated. Up to now the verdict must be "not proved." In a disease where a large portion of the cases have always reached latency without recognized symptoms of early disease, such evidence is less than conclusive even though suggestive. Certainly we do not know now and possibly never will know whether this inadvertent therapy is in balance more helpful than harmful in controlling the treponeme. I judge that for the community it is probably more helpful.

Finally, let us consider very briefly certain situations in which, in any country, treatment before clinical diagnosis may be justified. In such instances one might claim that an epidemiologic diagnosis had been established. For many years in most medical centers, it has been considered proper to treat immediately individuals who have been exposed to infection by such accidents as pricking of the finger with a contaminated needle. Even in the arsenical era treatment was administered in certain of these accidents by clinicians of undoubted eminence and competence. With the advent of the safer and more efficient antibiotics, the frequency with which this was done increased, and the criteria for taking such action were made less stringent, due attention being paid to the problem of sensitivity.

Now the matter of how far such prophylactic therapy can be reasonably and beneficially extended has become a subject of importance. Many experts will condone such practice in the case of the pregnant woman known to be a contact of infectious treponemal disease. Fewer, but still a great number, will recommend that all sexual contacts of cases of infectious syphilis be given therapy. In my mind there is no question that this latter course is justifiable as a community health measure. I believe that the hazards of potential psychological disturbances can be largely prevented by proper guidance and those of reactions to the antibiotic, by proper management. Clinical medicine is based on the weighing of probabilities in diagnosis and the possible benefits vs. possible harm in therapy. Each clinician and public health worker must make many decisions on this basis. So long as this is true and there are not absolute answers to all

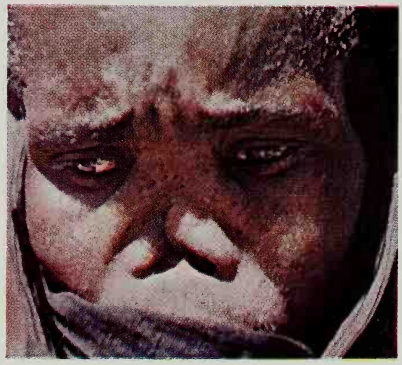
PLATE V

E. Patient with pinta. (From Medichrome series.)

F. Patient from Africa with endemic syphilis. (Courtesy C. J. Hackett, WHO, Geneva.)

Each patient shows typical "late secondary" nodular lesions with nearby dyschromic, macular lesions.

G. Patient with yaws. (From Medichrome series.)



H. Patient from Africa with endemic syphilis. (Courtesy C. J. Hackett, WHO, Geneva.)

Both patients demonstrate typical destructive late lesions, resulting from gummatous osteoperiostitis, which have involved the nasal bones and septums. The patient in H also has had involvement of the palate.

These illustrations demonstrate perfectly typical lesions in patients with pinta, endemic syphilis or yaws. In E and F are shown lesions in which treponemes can be demonstrated but are relatively noninfectious. In G and H are shown late, destructive manifestations.

diagnostic and therapeutic questions, there will be differences of opinion. In this particular instance it would appear to me that what is best for the community is also best for the patient.

SUMMARY AND CONCLUSIONS

Several problems related to the diagnosis of treponemal disease have been raised, some opinions expressed and no quick and easy solutions outlined. In the more developed areas of the world, great strides have been made since World War II in the control of venereal syphilis. While there has been evidence of increasing rates in most of these areas, the rates are probably still well below those of the middle 1940's. There is some evidence of renewed interest in the problem among the general public and public health officials which augurs, it is hoped, a new downward trend in the incidence of syphilis. In other areas, tremendous efforts have been directed toward the elimination of endemic syphilis, yaws and pinta. During the period 1950–1962, national mass campaigns have the following achievements to their credit: 285 million persons examined in surveys and resurveys in 45 countries; 38 million of these persons were treated with long-acting penicillin. In the rural areas of these countries, the prevalence of active cases dropped from 10–20 per cent to generally less than 0.5 per cent. Probably 100 million persons still live in endemic areas where 30 to 40 per cent of the population have treponemal infections and where little or no systematic control effort has been expended.[9]

While the practicing syphilologist seems to be a species doomed to extinction in this country, the treponematoses are still with us and will continue to be for some time, though in the long run the treponeme also, it is hoped, is doomed. Until this happy state of affairs is reached there will continue to be problems facing the health professions in their efforts to eliminate the treponeme. The problems will change in nature as progress is made toward the goal. Until that goal is attained it is essential that an adequate group of interested, well-trained and dedicated workers be available to carry on the good fight.

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New Laboratory Methods in the Diagnosis and Management of Syphilis

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REAGIN TESTS

Ever since the first report of the Wassermann reaction in 1906, the physician has often been faced with the problem of correctly interpreting and coordinating the results of various nontreponemal serological tests for syphilis with the clinical findings. Improvement in methods and materials, particularly the purification of antigen in the form of cardiolipin, has not eliminated the false positive reactions that sometimes occur with complement-fixation and flocculation tests. This is not surprising in view of the fact that all these tests are based on an empirical reaction between a nonspecific antigen, consisting of a lipoidal beef-heart extract, and a so-called antibody in syphilitic serum called reagin. It is now well appreciated that reagin is produced in response to a rather large number of acute and chronic conditions which can in turn produce "biologic false positive" tests for syphilis. With the concept in mind that a serological test merely detects the presence of antibody and does not diagnose syphilis, it seems a little odd to apply the term "specific" to the reagin tests at all. If they give positive reactions to reagin-containing serum due to any cause, they would necessarily be specific, though not for syphilis. This is not to underrate the value of the reagin tests as valuable diagnostic tests for syphilis. Indeed, in certain situations their value far outweighs that of the more glamorous treponemal tests, whose clinical value is limited to very narrowly defined limits. Research and developments in reagin testing have

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kept pace with those of treponemal testing and have enhanced their value to the physician. Most notable of these new developments has been in the area of rapid testing procedures.

Rapid Screening Tests

The first of the reagin tests was developed for the main purpose of accomplishing the rapid and economical screening of large numbers of persons. Time previously lost in allowing for clotting of blood and inactivation of serum by heating has been eliminated in the RAPID PLASMA REAGIN TEST[1] (RPR). The antigen suspension used is derived from basic VDRL antigen containing cardiolipin, lecithin and cholesterol. The principle of these tests is that a chemical, specifically choline chloride, is introduced into the antigen for the purpose of inactivating or inhibiting the substances in unheated plasma or serum which interfere with the clumping of antigen and antibody. An additional substance, ethylene dinitrilo tetracetic acid (EDTA), is added to prevent deterioration of the antigen.

Extension of the principles of the RPR test resulted in the PLASMACRIT TEST,[2] where plasma usually discarded after microhematocrit determination is used for serological testing, and the UNHEATED SERUM REAGIN TEST[3] (USR), which uses unheated serum for testing. This latter test has been suggested as a screening test for public health laboratories by eliminating the water bath, and saving time normally allocated to the half-hour heat inactivation of serum required in the VDRL test.

The ultimate in new nontreponemal rapid screening tests has been developed which can be completed in from four to eight minutes, and requires no test tubes, microscope or centrifuge. The test, the RPR CARD TEST,[4] utilizes the Brewer Plasma Collection Card and a modified RPR antigen. In the testing, three drops of blood from a finger prick are dropped onto a keyhole-shaped depression of a card, which is coated with an anticoagulant, and a lectin, a substance which agglutinates the cellular elements. After mixing with a toothpick in the circular area of the depression, the red and white cells clump, and the plasma will drain into the collection slot after tilting of the card. With a graduated capillary tube, the unheated plasma is transferred to a plastic coated card containing a series of teardrop depressions. A drop of antigen is added, using a needle and plastic dispenser. As stated, this antigen suspension is similar to that used in the other rapid reagin tests, except that it contains colloidal charcoal, which makes macroscopic reading possible. The antigen suspension and plasma are mixed thoroughly, spreading the mixture over the entire teardrop. The card is then tilted back and forth. Specimens showing clumping of carbon particles are read as reactive. Comparison of this test with standard reagin tests has shown excellent correlation, except for slightly increased sensitivity which is not an undesirable characteristic in a screening test.

Despite the definite limitation of the nontreponemal tests in detecting

only reagin, their value is almost undisputed in the following situations: (1) Because of their economy and relative ease of performance, they are invaluable as screening tests. To be remembered are the facts that negatives are to be expected in very early syphilis or in a certain percentage of cases of syphilis of many years' duration, and reactive results are found in certain acute and chronic illnesses. In the clinical evaluation, such things as age, past medical history including venereal disease history, serologic history, and physical findings are very important considerations in the correct interpretation of a reactive reagin test. (2) When correlated with history and clinical evidence of syphilis, a reactive test is confirmatory. (3) When used in conjunction with epidemiological investigations, reactive results in contacts, suspects or associates are highly significant. (4) When reactive in high or rapidly increasing titer, a reactive test is almost diagnostic of syphilis though occasionally false positive reactions are found in high titer. (5) When used to follow babies suspected of congenital syphilis, a good quantitative reagin test is an excellent diagnostic tool. (6) Finally, the serological response following treatment affords an excellent parameter of adequacy of treatment.

TREPONEMAL TESTS

The definite limitation of the reagin tests provided the constant impetus for the development of a serological test specific for syphilis. Naturally, this would be directed toward developing an antigen derived from the etiologic agent of the disease. Wassermann himself apparently had this in mind when he prepared his original antigen from syphilitic fetal liver. Many attempts prior to Nelson's description of the Treponema Pallidum Immobilization Test (TPI) in 1949 met with little success. Then, in less than 15 years, a host of tests have been developed, some of academic and research interest only, and some of proven clinical value. These developments are the ones usually brought to mind when one mentions new methods in the diagnosis and management of syphilis. Indeed, this tends to eclipse the efforts in the area of nontreponemal testing and gives one the feeling he is dealing with anachronisms. However, the treponemal tests themselves suffer from definite limitations. They do no more than inform of the immunological status of the patient and do not answer the question of whether or not he has syphilis. To understand and properly interpret results of treponemal testing, the concept of a multiplicity of antibodies arising during the course of syphilis, and knowledge of the temporal relationship between them are necessary. Because of this, it is improbable that there will ever be a single test technique that will detect all of these antibodies.

Treponemal testing has found its greatest value in one of the following three areas: (1) to help distinguish between biologic false positive and true

positive reagin tests for syphilis. It is interesting that in any series of so-called biologic false positives (BFP's) studied, about 50 per cent will ultimately prove to be due to syphilis; (2) to help establish a correct diagnosis in patients who have clinical evidence of syphilis, particularly late syphilis, but who have nonreactive blood and spinal fluid reagin tests, and (3) to assist in the diagnosis in patients who epidemiologically should have the disease, but who have negative clinical serological evidence. The latter refers to a diagnosis of syphilis in a marital partner, or a mother who is seronegative with a congenitally syphilitic child. With these indications for treponemal testing in mind, the next questions would be: (1) to what extent reactive results may be considered evidence of past or present syphilis, and (2) to what extent may nonreactive results be considered indicators for the absence of past or present syphilis? In other words, what is the specificity and sensitivity of the various treponemal tests? In the discussion to follow, a chronological presentation of the treponemal tests will be given. Points to be covered are a brief presentation of the test procedures, advantages and disadvantages of the test proper, and usefulness as a clinical and research test.

Treponema Pallidum Immobilization Test

The era of treponemal testing began in 1949 when Nelson and Mayer described the immobilization of treponemes by syphilitic serum in the presence of complement.[5] In the test itself, virulent *Treponema pallidum* are extracted from rabbit testicles and placed in survival media. The serum to be tested and complement are added and this is then allowed to incubate for a period of time. Following this, the percentage of treponemes immobilized as compared to controls are counted, with the result based on this count. In theory, the test is *simple*; in practice, it is *difficult*. Laboratories performing this test must maintain a rabbit colony for a ready source of living treponemes. Highly trained and skilled technicians are necessary to assure reproducibility of the test. It is important to emphasize that the TPI is no single test. Procedures vary from one laboratory to another. Some pretreat the rabbits with corticosteroids or x-ray as a means of reducing supposedly sensitized treponemes. Others do not. Differences are encountered in the amount of thioglycolate added to the survival media, amount of complement added, length of incubation time, and number of treponemes counted. Thus, results can vary on the basis of procedure performed. It is surprising how many supposedly TPI nonreactive bloods from one laboratory will be reactive in another. Some knowledge of the actual procedures should be available to persons interpreting results. Because of the difficulty of the technical procedure and the great cost involved, very few laboratories have adopted this test. Also, the variability inherent in a test, that must employ an antigen of unknown and variable sensitivity for each day's run, gives the serologist considerable uneasiness. Clinically, however, the TPI test, despite these technical problems, has

proved a tool of the first magnitude permitting the resolution of many diagnostic problems that have heretofore defied other serological techniques.[6, 7, 8, 9, 10] With the knowledge that the TPI may be nonreactive in two-thirds of patients with primary syphilis and one-third of patients with secondary syphilis, it can be stated that the TPI will be reactive in essentially all other stages of syphilis and, of course, other treponematoses.[11, 12, 13] Thus, it is readily applicable to the diagnostic categories initially outlined. Because of its great specificity, all subsequent treponemal tests have been compared to this test and it has subsequently become a sort of standard. From a practical standpoint, however, there still remained a need for a specific serological test, which could be performed in the average serological laboratory, would be highly reproducible, and could be performed with a minimum of materials.

Treponema Pallidum Agglutination Test

The first effort in this pursuit was in the study of agglutination of spirochetes by syphilitic sera. Prior to the years 1953–55, efforts in this area had always ended in failure because it had been found that *Treponema pallidum* spontaneously agglutinated. McLeod,[14] extending the work of Japanese investigators who found that treatment of *Treponema pallidum* with weak hypochlorite solution would destroy the tendency of spontaneous agglutination, showed that heating produced the same results. Subsequently, she developed a test, Treponema Pallidum Agglutination (TPA), based on this principle, which showed fair correlation with the TPI on initial selected sera. In the actual test, heat-killed treponemes were agglutinated by syphilitic sera in the presence of fresh bovine sera containing both complement and conglutin. On further evaluation, however, it was found that serum containing reagin unrelated to syphilis could agglutinate *Treponema pallidum* and hence the test lost its potential clinical value.[15]

Treponema Pallidum Immune Adherence Test

During this same period, Nelson[16] described the phenomenon of *adherence* of treponemes to erythrocytes, sensitized with syphilitic serum, in the presence of complement. Following gentle centrifugation, the red cells would drop to the bottom of the tube, taking treponemes with them in a reactive result. In a nonreactive result, darkfield examination of the supernate is positive for *Treponema pallidum*. Comparison of the test derived from this phenomenon, Treponema Pallidum Immune Adherence (TPIA), with the TPI has shown it to be roughly equivalent.[17, 18] There developed some problems in reading of the test concerning what constituted a negative, weakly reactive and reactive, but subsequent work helped solve some of this. In actual practice, this procedure suffered from at least one serious defect—that of requiring living virulent treponemes. However, in 1957, Miller[19] described the preparation of heat-killed organ-

isms suspended in saline, and preserved by thiomerosal (Merthiolate) solution, which potentially could extend widely the usefulness of this test. The literature contains no recent experience on this subject.

Treponema Pallidum Complement Fixation Test

The appearance of the Treponema Pallidum Complement Fixation Test (TPCF)[20] introduced a new concept in treponemal testing. This represented the first time that an antigenic moity was extracted from treponemes "defatted" by acetone and ether with a solution of desoxycholate. Immediately, certain difficulties became evident in that the source of this material (virulent living *Treponema pallidum*) was in short supply. More of a problem, however, was the rather large number of normal sera giving positive reactions to the test. The first problem was ameliorated to a degree, by the introduction of testing using small volumes of reagents,[21] but the second persisted with up to 13 per cent of nonsyphilitic sera giving false positive results.[22] Because of the attractive feature of this technique being so readily adaptable to the average serological laboratory, the antigen did become commercially available. More recent work by McLeod,[23] however, has indicated another potential difficulty with the TPCF antigen. She found that the injection of this material not only formed a TPCF antibody, but reagin as well. It could be postulated that this impure antigen could produce false positive reactions in reagin-containing serum—one of the clinical areas where a confirmatory test is most needed.

Treponema Pallidum Methylene Blue Test

In 1956, an interesting modification of the TPI was described. This test, called the Treponema Pallidum Methylene Blue Test (TPMB),[24] is based on the inhibition of staining of *Treponema pallidum*, once it has become sensitized or perhaps coated with antibody. The test is performed in the same manner as the TPI, except methylene blue is added at the end of the incubation period with readings dependent on staining or lack of staining of treponemes by the dye. The test has all of the advantages and disadvantages of the TPI and most believe it adds little to the original test, especially if one is dealing with motile treponemes. It is thought, though, that the test certainly merits more evaluation and testing with the exciting possibility in mind that perhaps dead or desiccated *Treponema pallidum* could be used in the test. With this, the simple presence or absence of red color (methylene blue stained organisms are red under darkfield light) in the organism could determine presence or absence of antibody, with lack of staining indicating a reactive result.

Whole-Body Treponema Pallidum Complement Fixation Test

Cohen, in 1956, introduced a complement fixation test, the Whole-Body Treponema Pallidum Complement Fixation Test (WTPCF),[25] using phenol-treated *Treponema pallidum* as an antigen in a one-fifth volume

Kolmer complement fixation test. The preliminary results reported in the paper are roughly in agreement with the TPI on a limited number of sera; however, no wide evaluation of the technique is available.

The year 1957 saw the introduction of a number of new procedures. Two of these, the Reiter Complement Fixation Test (RCFT) and the Treponemal Wassermann Reaction Test (TWR) have had little development and evaluation, while the other two, the Reiter Protein Complement Fixation Test (RPCF) and the Fluorescent Treponemal Antibody Test (FTA) have had extensive evaluation and application.

Reiter Complement Fixation Test

The Reiter Complement Fixation Test (RCFT)[26] employs as antigen a suspension of Reiter organisms in a phenol-saline solution. Testing technique is the one-fifth volume Kolmer. While the preliminary report showed that the test was more specific than the reagin tests in problem sera, and also more sensitive in late symptomatic and untreated early syphilis, its overall performance was far below that of the TPI. No further evaluations are available.

Treponemal Wassermann Reaction

The Treponemal Wassermann Reaction Test (TWR)[27, 28] enjoyed a brief period of popularity in the English literature as a test which compared favorably with the TPI in sensitivity and specificity, but which became reactive sooner than the TPI in early syphilis but also became nonreactive sooner than the TPI following successful treatment. The test utilized antigen derived from *Treponema pallidum* "cut up" with ground glass on a shaking machine in a complement fixation reaction. On further evaluation, however, the test was found to produce a large number of false positive results, and furthermore, the results were not reproducible.[29]

Reiter Protein Complement Fixation Test

Work by D'Allesandro and Dardanoni[30] on protein extracts from the nonpathogenic Reiter organism showed this material to be antigenic and capable of reacting with syphilitic sera. The protein antigen used in the Reiter Protein Complement Fixation Test (RPCF) is extracted by subjecting the organism to 75 freeze-thaw cycles in dry ice-acetone with subsequent precipitation of the protein using concentrated ammonium sulfate solution. The material so obtained is employed in a one-fifth volume Kolmer complement fixation test[31] (RPCF). To recommend its use, an inexpensive and readily available antigen is used and the basic testing procedure is performed in most laboratories. When this test was evaluated in the Public Health Service sponsored study designated as SERA or Serology Evaluation and Research Assembly, its sensitivity and specificity appeared to be quite satisfactory, being similar generally to the TPI test. Subsequently, because of the initial favorable evaluations, the test was

widely adopted by State public health laboratories to be performed as a sequel to the positive nontreponemal tests from patients not previously diagnosed as having syphilis. After several years of actual application, its value and limitations can be more adequately assessed. Unfortunately, the original enthusiasm, that the procedure might serve as a satisfactory substitute for the more complex and expensive TPI test, has been shown by more recent evaluation to be premature. The Reiter test has had a low correlation with the TPI test in the group of patients in which serologic confirmation is most needed; that is, in cases characterized by no clinical or historical evidence of syphilis and a reactive reagin test. This lack of good agreement apparently is the result of a lesser sensitivity of the Reiter test. In a study of syphilis of long standing in the male Negro, the RPCF was much less reactive than the TPI test; the difference was even greater in those patients having inadequate treatment than in those having had no treatment. On the basis of these and other studies, it was indicated that in interpreting results in syphilis of long duration, whether treated or untreated, the chances are that Reiter tests will be nonreactive more than 50 per cent of the time.[32, 33] Although most of the concern has been the lack of sensitivity, at least one recent report has pointed to the occurrence of biologic false positive reactions with the test.[34] Efforts to correct some of the shortcomings of the test have met with some success; for example, it has been found that the sensitivity can be increased following freezing and reheating of serums,[35] but in the light of very recent investigations, which show that the Reiter treponemes share common antigens not only with *Treponema pallidum* but also with mouth and saprophytic treponemes,[36] it is doubtful that the RPCF will ever achieve the initial high hopes for the test.

Fluorescent Treponemal Antibody Test

The Fluorescent Treponemal Antibody Test (FTA)[37] is, in principle, an application of the indirect fluorescent antibody procedure. Antigen consisting of a suspension of the Nichol's strain of *Treponema pallidum* is dried on a slide and overlaid with the unknown serum. Should it contain antibody, it will react with the organism, depositing an invisible layer of antibodies. This is then treated with a fluorescein-tagged antibody to human globulin. If globulin (syphilitic antibody) coated the treponeme, the tagged material reacts with it and the treponeme will fluoresce when viewed under ultraviolet light. If no globulin coated the treponeme, no tagged antibody reaction will occur and no fluorescence is observed. When first published, a 1:5 dilution of serum was employed, but with the discovery of a more efficient fluorescent conjugate, fluorescein isothiocyanate, it became necessary because of a large number of nonspecific reactions produced, to modify the test so that a 1:200 dilution of serum is used. This revised technique, the FTA-200,[38] was found to have a greater reproducibility than the original test. In addition, the high specificity has been

retained, but because of the dilutional factor, the sensitivity has been reduced. Studies[36] recently completed and currently in progress to increase the sensitivity without loss of specificity of the test are of considerable interest. These studies show that at least one antigen (Reiter protein antigen) is found to be a common or shared component of the four treponemes studied: *Treponema pallidum*, the Reiter treponeme, *Treponema zuelzerae*, a free growing mud treponeme, and *Treponema microdentium*. Through absorption studies, however, a specific antigen of each organism could be identified. It is possible that nonsyphilitic treponemal antibodies detected by the FTA test when a 1:5 dilution is used are due to the antibodies directed against the mouth treponemes. By absorption of the antibodies directed against these common antigens, it should be possible to greatly increase the sensitivity of the FTA test, making unnecessary the 1:200 dilution, as well as slightly increasing its specificity. Another problem with the FTA has been that of background fluorescence of debris. This problem seems near solution, however, with the suggestion that this debris may be counterstained with Evans Blue which fluoresces red under ultraviolet light, thus affording a good contrast to the specific green fluorescence.[39]

The advantages of this test are evident. Desiccated treponemes can be supplied to laboratories from a central supply laboratory, as well as the conjugated antihuman globulin. The greatest technical disadvantage at the moment is that of the cost of ultraviolet equipment, but with the continued growth of the fluorescent antibody technique as a research and diagnostic tool in other areas, purchase by laboratories is justified.

Initial evaluation of the FTA test has been very favorable even with the 1:200 serum dilution requirement. The development of antibody as shown by the technique closely parallels the presence of immobilizing antibody except that it appears much earlier in most cases.[40] The FTA gives highest titers in secondary syphilis and following treatment will show a reduction in titer, but over a much longer period than the VDRL, for example.

Other Tests

Despite the rather momentous significance of the tests just discussed, work continued on development of additional techniques. This work resulted in the Treponema Pallidum Cryolysis Protein Test (TPCP)[41] which is identical to the RPCF except that it uses the virulent *Treponema pallidum* as an antigen source and more recently (1961) the Reiter Fluorescent Treponemal Antibody Test (RFTA)[42] has appeared. Even though this and a later modification using hypochlorite washed organisms show some favorable reports,[43] the prediction would be, on the basis of the common antigen shared by Reiter, with other treponemes, that this test would ultimately prove to be nonspecific.

From this confusion of "alphabet soup" designations, it is hoped that

one test procedure will ultimately be devised that can best answer the needs of the clinician, as initially set forth in this paper. Despite certain limitations, however, the tools are available *now* for the proper diagnosis and management of the overwhelming majority of patients.

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A Glance in Both Directions— The Impact of Syphilis on the Family

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About 25 years ago when syphilis control was being vigorously promoted by the U.S. Public Health Service and the resulting long lines of patients registering for "arm shots" or "hip shots" were commonplace scenes in the outpatient departments of hospitals and departments of public health, a patient* who had faithfully carried out the whole painful plan of treatment stopped by to tell me she would be moving to a distant state. I have always remembered the terse profundity of her message. She said, "Thank you for everything and I hope I never see you again."

The patient, an intelligent woman in her early twenties, had been referred from the Obstetrical Clinic to the Syphilis Clinic because of a secondary recurrence. She had earlier received inadequate treatment from her private physician, having seemingly never had a clear understanding of the disease and the potential consequences. At referral she was four months pregnant.

With some hesitancy the patient revealed her history. A former unhappy marriage had ended in desertion at the end of three months. Two years afterward she married again and in the present marriage the couple had been happy. Shortly after the marriage, however, both she and her husband learned they had syphilis, but the disease had apparently been accepted as a result of the patient's previous misfortune. Therefore she was able to keep her anxiety in check until pregnancy occurred. Then she became terrified for fear her child would have syphilis and as a result might be deformed. The possibility of having a syphilitic child aggravated her guilt about her husband's infection. He, on the other hand, found it hard to understand the patient's fears since he was especially happy about the advent of a child. His consideration of her seemingly did nothing but increase her anxiety.

Reaching out to this patient with understanding and empathy calmed her momentarily and aroused her interest in asking questions in areas

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* The case illustrations are true accounts, sufficiently disguised to prevent identification.

which had been so anxiety provoking. It was a relief to her to learn from an authoritative agency, the hospital, that her chances of having a healthy baby were excellent and that, even should the child have syphilis, it could probably be "cured."

Throughout the rest of the pregnancy the patient's mental outlook improved markedly. She was able to pass on to her husband the education which she received. He, too, resumed antisyphilitic treatment. At the time of delivery, as was expected, the patient's anxiety increased, but by then she had developed confidence in her doctors and could also use well the supportive assistance of the social worker. Fortunately the child was a full-term, bouncing boy. From the day the patient stopped in to say good-by, I have not seen her. But we may hope with some confidence that the ghost of syphilis was laid in that family.

Another patient, a man in his forties, learned of his positive blood when he volunteered as a blood donor. He, too, had had antisyphilitic treatment many years earlier but not so long before his marriage that he could be advised to forget about the need for his wife to be examined as a contact. Should her blood be positive, there were five children who would also need examination. At first the patient was almost unable to face the threat to his whole way of life, but he did measure up to it. The couple, for the wife was found to be infected, began antisyphilitic treatment, and supported each other through the seemingly endless weeks while the children's status was being cleared. They had partial good fortune in that the children had negative examinations. Feeling the concern of the clinic staff for them during their ordeal, these patients also shared with them their happiness upon finding that the children had been spared.

The successful campaign against syphilis of the 1930's and 1940's eventually did away with the customary swarming Saturday morning clinics for school children. As we look back upon the heartbreak which it causes, it is certainly to be hoped that the opportunity for congenital syphilis to develop will never occur again. One poignant example could be multiplied many times over.

A very bright high school graduate moved from her small town to the city to go to work. In the course of a routine examination she was found to have a positive blood and, in exploring her history, it was learned that as a young child she had had "shots" for a diagnosis unknown to her. A younger sister apparently had juvenile paresis but the etiology of the psychosis was unknown to the patient. Later her mother wrote:

> "I appreciated the nice letter you wrote concerning Mary's treatments. The reason I have kept this a secret from her, I thought she might be cured without having to know how handicapped she was. It's been such a great burden to me, that I didn't want her to suffer what I had suffered.
>
> "It's her father's fault and ignorance on my part that this happened. It is strange at my age I was so ignorant of these things but my mother failed to teach me and I happened not to learn otherwise, and so it's almost wrecked my home and life.
>
> "I hope you people will do your best for her. She has tried so hard to

accomplish something worthwhile. I hope she can set aside the thought of her condition and not feel so handicapped. How long do you think she will have to continue the treatments? My husband and I took a blood test about four years ago. It proved negative. I have been extremely careful since I learned about the disease.

"Each of us has taken the blood test except the youngest daughter. She is 15 years of age and seems to have perfect health. Do you think it necessary for her to have a blood test? I'll be so thankful for any advice you may be able to give us."

This letter from a mother who had never met any of the clinic staff but was merely responding to a note expressing interest in her child whose ability held a considerable degree of future promise, needs no comment. It reveals the lack of information, the misinformation and the years of tragedy constantly hovering over the family. Notable in the tragedy is the fact that so much of it might have been prevented, since it is not necessarily the disease itself which does much of the harm, but rather the consequent impairment of family relationships. A woman who could so simply, so concisely, and yet so feelingly recount her misery from her own viewpoint, could probably have solved or at least diluted her emotional stress had she been able to share this with an informed, sympathetic person who would take time to listen. "Taking time" is a carefully chosen statement; it is extremely easy in a busy workday not to have time to take on oneself the emotional turmoil of others. To do so is sometimes itself anxiety-producing; it is demanding also, but will the job of syphilis control be accomplished unless dealing with the emotional component is fully accepted as a part of the challenge?

One of the more articulate patients once informed me of the effect that he felt from the nonjudgmental attitude of the social worker. Because of his feeling of disgrace and the consequent severe emotional reaction, he could not discuss with anyone the fears and anxieties which he had been secretly storing away in his mind for several months. Until he realized that the social worker was not judging him, he reacted defensively. He would slink into the hospital, thinking that everyone who saw him enter said, "There goes John. He has syphilis." He later remarked that the social worker's acceptance of him had helped him immensely to face the situation with some objectivity and to try to plan a constructive future. In a sense, the social worker represented public opinion.

In analyzing the difficult situations which patients with syphilis in earlier days had to meet we could group them into three broad classifications:

(1) Those within the personality of the patient himself.

(2) Those which concerned the patient's relationship with his family, including the marital problems, fear of having other members of the family learn the diagnosis, the wish to avoid causing discord at home because of unusual precautions against spreading infection, and the problems concerned with the examination of household contacts.

(3) Those which concerned the patient and the community, including the patient's work and school arrangements to permit clinic attendance, his plans for remaining away from work during the infectious stage, and the necessity for examination of contacts outside the home.

What differences do we perceive today? With the development of short and less arduous treatment methods, greater ease of obtaining treatment, most often by arranging a convenient appointment with a private physician, many of the practical difficulties have solved themselves. Work and school schedules are seldom upset, infectiousness is rapidly controlled, easy transportation is generally available, and despite the great increase in the cost of living, more people can afford the expense of present-day therapy. Still to be met, however, are the problems caused by the diagnosis of syphilis as it affects the patient's personality, his relationships with his family, some of whom may also need to be considered as household contacts, and the problem of examination of extramarital contacts. Despite the fact that today sex is dinner table conversation and our literature and films would give the impression that there is little inhibition left, the patient who is informed he has syphilis does not as a rule take it casually. We might well recognize in the case illustrations from an earlier time some of the reactions of today's patients.

The more sophisticated patient would perhaps now be unlikely to put much credence in any talk of easy "innocent" infection. All to the good. The doctor, nurse, investigator or social worker ought likewise now be able to face the truth more comfortably with the patient and thereby more quickly set the stage for a relationship of confidence. For, with the concrete difficulties being, in the main, solved, the therapeutic importance of the relationship of the patient with the medical and paramedical personnel becomes highlighted. Most of the patients will not seek psychiatric care; we know such attention could not be made available to the majority of patients. The patient will, though, seek the solution of his distress in the treatment clinic or in the doctor's office. Moreover, for the contact investigator the relationship with the patient is of more than humanitarian interest. It is, in fact, the only tool whereby he can obtain information. The law cannot force the patient to give data about contacts, but experience has shown that the respected patient will usually rise to the request made of him.

A final word. The enthusiasm of the campaign to "stamp out syphilis" was perhaps as infectious as the disease itself. It was a challenge to find contacts with only the briefest of descriptions and the address of the "hangout." It was even more satisfying to have them request examinations. Many of them turned into truly grateful patients. With the patient load being more scattered it is harder now to recapture the same enthusiasm, but I am convinced that this is an essential ingredient.

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Penicillin Fallout and Infectious Syphilis

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In May, 1962, the *Pennsylvania Medical Journal* published a short article entitled "Penicillin Fallout—Menace or Manna?"[1] It called attention to two phenomena which no doubt have been observed by many physicians:

1. Penicillin administered to treat one clinically manifest ailment often cures simultaneously a second coexisting disease.

2. During the years (1948–1953) when millions of people were receiving penicillin administered (often on slight indication) for a multitude of ailments, certain major diseases formerly common virtually vanished from the scene. Included in this group were lobar pneumonia, hematogenous osteomyelitis, meningococcic and certain streptococcic infections, suppurative parotitis and syphilis.

Piecing together these two observations, it was suggested that perhaps the near disappearance of these serious diseases was not due primarily to penicillin treatment of clinically manifest cases of these diseases. Rather, penicillin reached *unrecognized* early cases and asymptomatic carriers who chanced to be ill at the time with an intercurrent ailment for which the penicillin was administered. Such "happenstance" treatment not only aborted the disease in the individual; what was more important from the public health standpoint, it abbreviated or eliminated his period of infectiousness to others. As a result, spread of the disease was curbed and the incidence of new cases declined.

Taking infectious syphilis as an example, it was noted that, during the years when penicillin was most widely employed for myriad ills, the syphilis attack rate declined by 93 per cent. Subsequently, as physicians became ever more selective in their use of the drug, the annual number of reported early cases promptly tripled.

These "off-beat" comments evoked a number of responses, some of approval, some of dissent. One of the most interesting, and certainly the best formulated, is entitled "An Answer to Penicillin Fallout . . . Menace or Manna?" by Popper.[2] Briefly his thesis is:

1. "Happenstance" treatment of early syphilis is inadequate treatment.

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2. Such inadequate treatment is worse than no treatment at all, for, by suppressing the clinical and serologic manifestations, early diagnosis and adequate treatment are prevented.

3. Penicillin administered four or more years after infection cannot change the course of the disease.

4. The hope of eradicating syphilis lies in "reassigning" its diagnosis and treatment to the specialist in dermatology and syphilology, as was the case before the advent of penicillin. "The possession of a syringe and a bottle of penicillin is not enough."

If the reconciling of these differing views were simply a matter of academic concern, further discussion would be contentious and pointless. But there is more at stake here. For it is just possible that within this "happenstance" concept there may be hidden, like a pearl within an oyster, the clue to the extermination of syphilis. It becomes obligatory, therefore, to point out that other syphilologists have presented data that are at variance with the views Popper expresses. Let us examine each of his four points.

1. Regarding the question of the inability of "happenstance" penicillin to cure early syphilis, it seems unlikely that Popper believes that the patient with a major illness treated with 600,000 units of penicillin a day for eight or ten days would not be cured of concurrent early syphilis. Surely this dosage (more than twice the 2.4 million unit minimum effective dose recommended for early syphilis) is adequate.[3] But there does exist room for doubt as to the adequacy of two or three injections of 300,000 units, given for a coincidental illness of lesser gravity. Nevertheless, the investigations of Alexander, Schoch and Mantooth,[4] Rein and Kitchen,[5] and Merrell[6] demonstrate that the vast majority of cases of early syphilis *can* be aborted by surprisingly modest doses of penicillin. Merrell's series of 7485 patients, tabulated according to the types and amounts of penicillin received, indicates that 82 per cent of the cases of primary and secondary syphilis treated with as little as 300,000 units remained free of evidence of clinical or serologic relapse over a post-treatment observation period of 18 months. As the dosage increased, moreover, the relapse rate declined sharply. Had penicillin reached these persons in the incubation period, an even better cure rate seems likely.

2. Anent the statement that "happenstance" treatment is worse than no treatment at all, Willcox[7] states that the fear of masking syphilis by the penicillin treatment of gonorrhea "proved a bugbear." "Either the disease was aborted completely, or it declared itself within the usual three months. In fact, the disease was usually cured in the incubation period, and the enormous decline in the numbers of cases of early syphilis (a fall of 95 per cent in the clinics of England and Wales between 1946 and 1956) has probably been achieved because of the enormous use of penicillin for gonorrhea and other diseases, which cut it off in this way." Delacretaz[8] concurs: "This notion of arrested syphilis, which seems a widely accepted

one, is based exclusively on disputable observations, as Durel and his collaborators have demonstrated."

3. In the light of the opinions reported in the two preceding paragraphs, Popper's third point (that penicillin is ineffective in late latent and late syphilis) ceases to be germane to the discussion. Therefore, the evidence to support a contrary view will not be gone into here.

4. I agree with Doctor Popper that in the treatment of syphilis the mere possession of a syringe and a bottle of penicillin is definitely not enough. Syphilis is a complicated disease, often difficult of diagnosis, variable in its course, uncertain as to its outcome. Should I ever contract the disease myself, I would hasten to consult my favorite syphilologist, knowing that he is best qualified to deal with it, and would wish that *every* known syphilitic was in fact receiving expert care at the hands of a syphilologist. Would this be enough? Would this bring us closer to elimination of the disease, or even its control? Moore suggests not. "Never in the history of medicine has any infectious disease been eradicated, or its incidence even partially controlled, by the sole process of treatment of infected persons."[9]

From 1944 through 1947, the massive assault on syphilis might have been expected to exert a profound effect in lowering its incidence. Nearly ideal conditions prevailed:

(*a*) Throughout the nation there was a vast network of Rapid Treatment Centers, manned by experts.[10]

(*b*) Record federal appropriations for venereal disease (up to 17 million dollars annually) brought treatment within reach of all diagnosed cases, and made possible unprecedented epidemiologic activity.[11]

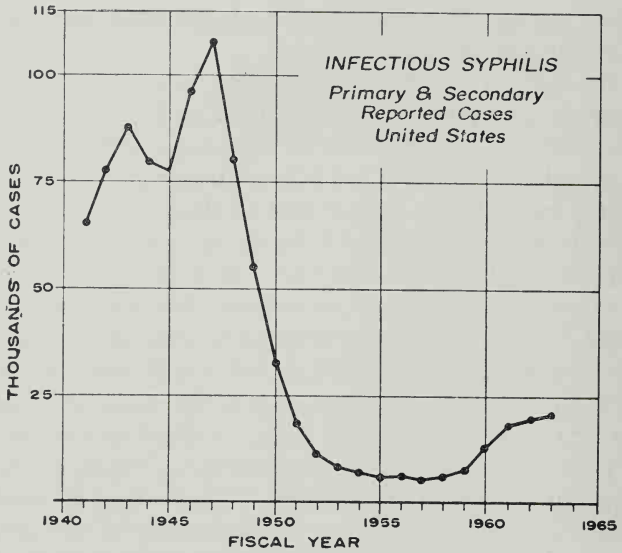
(*c*) Penicillin, then in short supply, was allocated with high priority to the venereal disease program, but was not available (in any form practical for widespread use) to most of the general physicians throughout the country.[12]

(*d*) As a result, almost all of the many thousands of cases of diagnosed early syphilis were treated by specialists.

The tremendous good that was accomplished during those four years by this gigantic effort stands to the credit of the Public Health Service and its co-operating organizations. Nevertheless, despite the cure of thousands of syphilitics whose disease had been diagnosed early, and despite treatment of their known contacts, instead of declining the reported incidence of infectious syphilis actually increased by 35 per cent—from 78,400 cases in 1944 to an all-time high of 106,600 cases in 1947.[13]*

In 1948, the average practicing physician was first able to obtain a convenient, practical, "safe" preparation of penicillin with which to load

* That this increase was actual rather than "statistical" is suggested by the fact that the increased reporting and epidemiologic activity required to produce an "epidemic of reports rather than of disease" would be expected to bring to light, simultaneously, increased numbers of early latent, late latent and late cases previously missed. (These normally outnumber early cases by a wide margin.) Instead, there was an actual decrease in reported cases in these categories.[13]



SOURCE: USPHS VD FACT SHEETS

Figure 1

his syringe.[12] This he employed almost not at all in the treatment of diagnosed syphilis. He did use it generously to treat a vast assortment of nonsyphilitic infections, minor as well as major. It is inevitable that many an *unrecognized* early syphilitic, treated for one of these *other* ailments, had his asymptomatic syphilis cured as a side effect. Significantly, it was in that same year that the syphilis attack rate began its precipitous 93 per cent decline (Fig. 1).

To be sure, other important factors also were operating during this post-war period. Nonetheless, analysis of these trends offers little to sustain the premise that the ultimate elimination of infectious syphilis will result from treatment (no matter how expert) which is limited to diagnosed cases and their known contacts. Too many early infectious syphilitics remain (and will continue to remain) undiagnosed, and too many contacts remain (and will continue to remain) unidentified, despite the best efforts of public and private medicine.

Heyman,[3] very concisely, has stated the reason: "Infection without noticeable lesions probably occurs in a high percentage of cases." These persons, and those with the scanty, insignificant primary and banal secondary lesions described by Manson and Trice,[14] rarely reach a syphilologist or any other physician *for diagnosis and treatment of early syphilis*, but they may be fortunate enough to incur some intercurrent illness for which penicillin is administered. Failing such "happenstance" cure, these persons remain free to seed their disease to who knows how many others. When these undiagnosed—better yet, undiagnosable— cases escape therapy

the incidence curve climbs. When penicillin reaches them, by whatever means, the curve falls.

If we accept "happenstance" penicillin as the major explanation for the decline in the syphilis attack rate in the 1947–1953 period, and lessened use of penicillin as the major factor in the recent recrudescence of syphilis, one conclusion seems inescapable: Now that physicians, because of human reactions and resistance of organisms, are turning from the widespread use of penicillin, opportunity for "happenstance" cure of syphilis is decreasing and a continuing rise is expectable.

In 1956, Pillsbury[15] said: "It has been assumed by many observers that the suppression of syphilis has resulted principally from early diagnosis and treatment, the searching out and treatment of infected contacts of patients with early syphilis, and adequate follow-up studies to detect relapse. That these measures are highly important cannot be doubted. It is our belief, however, that the suppression of syphilis has occurred *principally* as a result of intermittent treatment of the entire population with spirocheticidal drugs . . . administered for a variety of reasons, but all having as a side effect the suppression of undetected active or latent syphilis." Pillsbury further commented: "Concern may be felt, however, in regard to the decreasing applicability of penicillin to the general population because of sensitivity induced by repeated administration."

If these views are correct, and "happenstance" penicillin (rather than the public health program) was indeed the real hero of the 1947–1953 decline in incidence of infectious syphilis, it is of utmost importance that this be recognized. The reasons follow.

1. A blueprint for the eradication of syphilis in the United States is outlined in the report of the Surgeon General's Task Force.[10] This plan, probably the only practical one possible at this time, calls for a program that should result in a further reduction of syphilis mortality and morbidity (especially in the late stages). The program is very important and deserves the full support of both the profession and the public. Basically, however, it is similar to the program carried out since 1937, in that it brings treatment only to *diagnosed* syphilitics and their locatable contacts. It is questionable whether any program (no matter how vigorously promoted) that fails to bring treatment to the *undiagnosable* early syphilitic can carry incidence to the vanishing point, as "happenstance" penicillin almost succeeded in doing in the early fifties.

2. If the key to the conquest of syphilis is treatment of the undiagnosed early infectious cases—those in the incubation period, those with hidden or atypical lesions overlooked by both patient and physician, those too unconcerned to seek diagnosis and treatment—in short, those who escape the diagnostic and epidemiologic dragnet, one wonders as to the appropriateness of the word "eradication" in this connection. Its Latin prefix and stem (*e* out + *radix, radicis,* root) suggest the painstaking pulling out by the roots of weeds in a garden—weeds that must be iden-

tified as such before they may be plucked. To be sure, there is great value in this process, for it maintains a measure of control. But week after week, year after year, the process must be repeated, because of the maturing of the invisible seeds which were not destroyed in the previous weeding. Were it possible, however, to render the soil unfavorable to the growth of the seeds, eradication would cease to be necessary. Automatically the result would be extermination (*ex* out + *terminus* limit, end).

So it is with syphilis. Great effort is expended to trace down all known and suspected cases of syphilis, but, as every experienced epidemiologist knows, it is an endless task.

In an article entitled "The Vicious Chain," Warshofsky[16] recounts the experiences of an able venereal disease investigator tracing the chain of infection started by a 16 year old boy named Victor. Some 96 teen-agers are interviewed. Of these, 18 are found to have syphilis. Undoubtedly many others have been spared the disease because of prompt apprehension and treatment of these early infectious cases. After almost three months of dedicated effort, the public health worker dares to hope that he may soon reach the end of the trail. Not so, for with dramatic suddenness the track leads back to Victor! Ironically, the chain of infection he started has twisted around to reinfect him. And already he has exposed five new contacts!

What reader of Warshofsky's account can fail to be impressed with (1) the tremendous value of the Public Health Program as a means of *maintaining control* of syphilis mortality and morbidity, and, at the same time, (2) its Sisyphus-like futility as a means of *eliminating* the disease from the land?

During those years, however, when the population was fairly saturated with penicillin (administered for nonsyphilitic ailments) the treponeme found survival difficult, because its human host was often uninhabitable to the organism. Had it been possible, within the space of a few days, to have "penicillinized" *every* person in the population, syphilis (and perhaps a number of other diseases) might have been wiped out almost overnight.

For many reasons, there is not at the present time any practical way of accomplishing a near-simultaneous mass prophylaxis of the entire population so as to deprive every treponeme of its every host and potential host. Nevertheless, physicians concerned with syphilis control would do well to give serious thought now to devising a plan to be put into effect promptly when the next safe, convenient, inexpensive spirocheticidal remedy is brought forth by the pharmaceutical industry. Such a drug, properly distributed, *before* the population has time to develop allergies to it, and *before* organisms have time to develop resistance against it, could conceivably exterminate the great pox—and, simultaneously, by "happenstance" in reverse, perhaps some other equally important diseases.

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Gonorrhea: Present Knowledge, Research and Control Efforts

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YESTERDAY

For such an ancient and prevalent disease, advances in the knowledge of gonorrhea have come about very slowly. While medical historians are not in agreement,[7] it is believed by some that its venereal character was known to the early Jews and described in Leviticus XV. Galen in A.D. 130 was responsible for the name "gonorrhea," meaning "flow of seed." The first description of a contagious urethritis recognizable as the gonorrhea of today is recorded in a manuscript in 1376 by John of Arderne, surgeon to Richard II and Henry IV. Both Paracelsus, 1530, and John Hunter, 1767, believed and taught that gonorrhea was a symptom of syphilis. Hunter's strong belief came about after he inoculated himself with gonorrheal pus from a patient with concurrent syphilis and developed both diseases. It was not until 1860 that Phillippe Ricord unraveled this misconception and clearly differentiated these diseases.

In 1879, long after Anthony van Leeuwenhoek discovered the microscope, A. Neisser identified the etiologic agent as a diplococcus and named it gonococcus. Gram's staining technique in 1884 aided in the microscopic presumptive identification of the organism. In 1885, Bumm grew the organism on artificial medium and showed that pure cultures, when inoculated intraurethrally, could cause the disease. The histopathology of the disease was described in 1894 by Finger, Ghon and Schlagenhaufer, and the first complement-fixation test was described by Muller and Openheim in 1906.

In 1881, Crede showed that gonococcal ophthalmia neonatorum could

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be prevented by routine use of silver nitrate solution in the eyes of the newborn. Treatment of gonorrhea with sandalwood oil was discontinued when Jonet in 1892 introduced potassium permanganate solution. For many years the local application of antiseptics by irrigations and instillations was the therapeutic rule. Today, their value is not accepted, and it is felt that their use may also have contributed to complications of the disease process.

Almost forgotten in this day of antibiotic and chemotherapeutic agents was treatment with vaccines and cultural filtrates. While championed by some, they were probably of little value. Domagk's discovery in 1932 of the curative action of the azo dye, Prontosil, ushered in the era of specific chemotherapeutics. At first, the gonococcus succumbed to sulfonamide action but, during the seven years before penicillin became available, gonococcal strains developed resistance to concentrations in excess of those tolerated by the host.[26] Just when despair was greatest of ever finding a substitute for the once successful sulfonamides, penicillin burst forth as the almost perfect therapeutic agent. So effective was penicillin in the treatment of gonorrhea that competent observers suggested in 1943 that 160,000 units of penicillin over a 45-hour period represented the use of an excessive amount of the drug.

In a short time, however, Venereal Disease Program statisticians pointed out that the reduction in syphilis morbidity noted after 1947 was proportionately much greater than that observed in gonorrhea. As early syphilis morbidity decreased, public health workers, alarmed by the continuing high gonorrhea morbidity, began to devote more time and effort to the control of this disease.

A system known as *speed zone epidemiology* was introduced in December, 1952 in Washington, D. C. During the next few months, this plan went into effect in Memphis, Chicago, Jacksonville, Norfolk, Philadelphia, Atlanta, San Francisco, New York City and St. Louis. Male patients with gonorrhea were interviewed for relevant contacts, and every effort was made to bring the contacts to examination and treatment within 72 hours of their being named. Eighty per cent or more of the contacts of male volunteers in most participating clinics were brought to examination and treatment within the prescribed period. However, the number of male volunteers with gonorrheal urethritis attending the clinics remained essentially the same.

In 1956, *antibiotic quarantine* was combined with *speed zone epidemiology* in a report by Hookings and Graves.[11] Antibiotic quarantine involved the use of benzathine penicillin G to maintain prolonged blood levels in an effort to prevent reinfection for a period of two to six weeks, depending upon the dosage employed. Following this report, speed zone epidemiology and antibiotic quarantine were widely applied in major metropolitan area venereal disease clinics around the country. Despite enthusiastic applica-

tion for several years in different sections of the country, it became apparent that the incidence of gonorrhea was not being significantly reduced.

TODAY

Today we have awakened to the realization that even by employing the most effective therapeutic agent ever discovered, combined with vigorous case-finding efforts, control of gonorrhea has failed. The incidence of this disease with little or no immunity and a short incubation period is now climbing after a slight decline following the war years. Contributing to the total number of cases today is the increased rate among teen-agers. A recent national survey of venereal disease cases treated by physicians in private practice[4] indicates that 70 per cent of the cases are treated outside public clinics but only 10 per cent of these cases are reported. The true incidence of the disease is unknown, but it is conservatively estimated that 1.5 million new cases occur annually in the United States.

Causes of Treatment Failure

For a decade, it seemed unlikely that the gonococcus would become resistant to penicillin as it had to sulfonamides. Long-acting preparations of procaine and benzathine salts of penicillin replaced multiple doses of sodium penicillin. Prolonged low blood levels from repository preparations selectively killed the more highly sensitive strains leaving the less sensitive ones to experience growth in residual amounts of penicillin below their minimal lethal concentration (MLC). Such penicillin experience known to slowly induce resistance *in vitro* gradually did so *in vivo*.

From 1945 to 1954,[9] susceptibility studies of 771 cultures of gonococci had shown all but five strains to be sensitive to 0.05 u./ml. or less. In 1955, Thayer et al.[25] in trying to explain the high failure rate of female gonorrhea treated with 600,000 units of procaine penicillin in oil with aluminum monostearate (PAM) discovered by sensitivity tests of the patients' cultures lower susceptibilities than heretofore described. Twenty-two per cent of the strains required 0.10 to 0.20 u./ml. to inhibit growth, a finding probably related to the failure of penicillin in the dosage used to cure the disease.

Surveillance studies of treatment failure cases since that time have shown that the range of penicillin required to prevent *in vitro* growth is slowly expanding over that noted in the early days of penicillin therapy and that the greatest proportion of evolving resistant strains is shifting within the range toward the higher concentrations. Today some isolates require over 1.0 u./ml. to inhibit *in vitro* growth.[28]

It is tempting to ascribe penicillin failure to the single fact of increased resistance shown by some gonococcal strains, but this would not account for other hypotheses or for some known facts.

In considering the successful treatment of gonorrhea, the relationship of penicillin blood concentration to the MLC for the infecting gonococcus is governed by the time required to effect a bactericidal response at foci of infection. *In vitro* this time has been shown to be 10 to 12 hours exposure to kill all but 0.01 per cent or less of the viable cocci. However, 36 hours have been required to sterilize the "persistors" in some cultures.[28]

Penicillin blood concentrations developed by individual patients given an intramuscular injection of 600,000 units of PAM vary widely. For 98 patients so treated, concentrations varied from 0.025 to 0.54 u./ml. at 24 hours, 9 per cent were below 0.10 and 50 per cent below 0.20 u./ml. at this time.[27]

A similar examination by Wright et al.[31] of blood concentrations developed by 35 subjects injected with 1.2 mega units of benzathine penicillin G also showed wide variability. The concentrations at 24 hours for these patients varied from an undetectable amount in one patient to a maximum of 0.45 u./ml. At this time, 50 per cent of the patients had levels below 0.10 u./ml.

Since gonococci *in vitro* will survive and multiply in concentrations of penicillin below their MLC, it can be seen that the opportunity for survival may occur in patients whose blood concentrations are inordinately low. It can be supposed that therapeutic failure would then result if other factors of host immunity and resistance do not enter the picture.

It may also be possible that when the gonococcal strain is relatively resistant to penicillin—say 0.45 u./ml.—it may be readily killed by the excessively high blood concentrations developed by some patients, thus resulting in successful therapy and removal of the resistant gonococcal strain from the venereal pool. Generally, the more resistant the gonococcal strain, the greater likelihood of therapeutic failure.

Patients harboring strains of gonococci most resistant to penicillin have been exposed to prostitutes outside the United States who receive low doses of benzathine penicillin at semimonthly intervals as a prophylactic measure against syphilis. While this treatment seems effective in preventing syphilis and decreases the incidence of symptomatic gonorrhea in those treated, the presence of subinhibitory concentrations of penicillin in these women undoubtedly contributes to the development of resistance with some strains of gonococci.[8]

To eradicate and prevent the further appearance of penicillin-resistant gonococci as hypothesized by Garson in 1957[6] seems today to be an impossible task. In 1957, a serum concentration of 0.35 u./ml. would have been in excess of the highest MLC for any known gonococcal strain in this country; today, a blood concentration of 2.0 u./ml. would be needed to satisfy the tenets of the hypothesis based on the finding of gonococcal strains with MLC's above 1.0 u./ml.

Apparent treatment failure at times may be due to reinfection when the patient returns immediately to his untreated sex partner(s). Failure

may also be falsely ascribed to penicillin when diagnostic methods are not used to rule out all possible causes of nongonococcal urethritis.

Two other possible causes of treatment failure have been put forward. The first concerns mistaken diagnosis of the *Mima-Herellea* group of microorganisms for *N. gonorrhoeae*. The second is that penicillinase-producing bacteria destroy penicillin at foci of infection and thus protect and allow gonococci to reinfect the patient. It seems unlikely, however, that these hypotheses can account for the major proportion of treatment failure.

Microscopically, the morphology of the gonococcus and *Mimeae* organisms appear quite similar in exudates and from growth on enriched media. Differentiation can be easily made on meat extract agar, unenriched broth or eosin-methylene blue agar media upon which the gonococcus does not grow. Fermentation reactions and other more difficult laboratory procedures are necessary only to determine species. Where gonococcal fluorescent antibody procedures are available, differentiation is rapidly made. Since Svihus et al.[22] in 1961 reported a gonorrhea-like syndrome caused by *Mimeae* in Italy, no other outbreak has been reported although Sokoloff and Goldstein[21] specifically looked for *Mima-Herellea* organisms in 195 men with acute urethritis without finding any. A substantial number of the men in the study were military personnel who had been in the Far East or Europe. When treated, none of the failure cases was due to *Mimeae*. The authors state that their "clinical findings correlated with *in vitro* results: No treatment failures were found among patients infected with an organism classified as 'sensitive' *in vitro*; all failures resulted among patients that had been classified as 'relatively resistant' by *in vitro* means." They further state, "Our studies, both *in vitro* and *in vivo*, support and document the opinion that the relative resistance to penicillin *N. gonorrhoeae* now displays is the single causative factor of its frequently reported failure to yield to the usual penicillin regimen."

Unfortunately, Sokoloff did not examine the penicillinase hypothesis first suggested by Hagerman[10] as the cause of treatment failure in women with gonorrheal proctitis. Bang[1] could not substantiate the hypothesis as it relates to the gram-negative penicillinase-producing bacterial flora of the rectum. More recently, Sanders et al.[20] have considered concomitantly growing *Staphylococcus epidermidis* found by them in urethral exudates of acute gonorrhea of the male to be more significant in treatment failure than relatively penicillin-resistant gonococci. Their laboratory exercise showing gonococci growing as satellite colonies around staphylococcal colonies composed of billions of penicillinase-producing organisms has prompted King[13] to question whether the static agar culture demonstration can be representative of the dynamic conditions of the vital process. Huge quantities of penicillinase would be required to continually destroy the intimacy of circulating penicillin and gonococci at foci of infection.

Another possible reason for some treatment failure, especially in the female, is that gonococci phagocytized by macrophages and columnar

epithelium remain viable and protected from extracellular antibiotic. It is hypothesized that in time with extrusion of gonococci or dissolution of the host cell viable gonococci are available for auto-infection of the host. Thayer et al.[23, 24] have demonstrated the possibility of such an occurrence by tissue culture studies; however, clinical research to prove the inference has not been tried.

A significant factor in the failure to control gonorrhea is our inability to diagnose the majority of infected females or to bacteriologically determine their cure following treatment. Though complications of gonorrhea in women—particularly acute and chronic pelvic inflammatory disease—are well recognized, clinically the female usually shows few signs and very frequently is asymptomatic. Treatment, based on epidemiologic findings (contact with an infected male), becomes necessary and acceptable for the reason that present laboratory procedures are not rapid enough nor are they completely effective in demonstrating gonococci in specimens. Bacteriologic culture procedures performed even under *ideal* conditions of the research laboratory are seldom able to demonstrate gonococci in more than 50 to 60 per cent of bona fide female contacts. Recent studies by Pariser and associates[16] document the existence of asymptomatic male genitourinary tract carriers to compound our problems. That the asymptomatic female is capable of disseminating the disease has been proved experimentally.[3] The epidemiologic importance of the infected male with no clinical evidence of disease must now be investigated.

Diagnostic Advances

An outstanding diagnostic advance is the immunofluorescent method for detection and identification of gonococci in exudate. The procedure, developed by Deacon et al.[5] in 1959, employs an immediate direct fluorescent antibody (FA) method and a delayed FA technique. In the former, complete identification as *N. gonorrhoeae* may be obtained within one hour. The delayed FA method, which is more effective for diagnosing the asymptomatic female, requires a 16- to 20-hour preliminary cultivation of exudate to accumulate gonococci in sufficient numbers for detection by fluorescent microscopy. The chief advantages of the delayed FA procedure over the clinical culture method are the time required to make a definitive diagnosis—16 to 20 hours against two to ten days—and the greater sensitivity of the technique in most laboratories.

In a field evaluation of the FA method by local public health and university laboratories in cooperation with the Venereal Disease Branch, Communicable Disease Center,[17] over 85,000 specimens from urethral, cervical and vaginal sites of 9483 females were examined. Using immediate direct and delayed FA methods and the classical culture method, gonococci were detected by culture in 22 per cent, by delayed FA in 37 per cent and by direct FA in 15 per cent. When female contacts of known gonorrhea

were studied, the culture was positive in 59 per cent, immediate FA 43 per cent and delayed FA in 79 per cent of 1782 patients.

Much work and study have gone into the development of a serologic test so urgently needed for diagnosis of gonorrhea. As yet, however, tests are not sufficiently reliable to be used in diagnosis due to poor specificity and sensitivity. Brown[2] recently reported a complement-fixation test using a salt-extracted antigen and found only 35 per cent reactivity among 164 men with acute gonorrheal urethritis. Among 51 culturally positive females in a penal institution, 72.5 per cent were reactive; but, of 189 women negative by culture, 40.7 per cent reacted. It would seem that this latter group should have been restudied culturally, for Mahoney et al.,[14] in studying in 1942 the natural course of the disease in untreated, asymptomatic females, found that cultures may spontaneously reverse from positive to negative. Furthermore, sporadic positive cultures may appear after a relatively long series of negative cultures. Control of gonorrhea will be greatly advanced when an adequate serologic test becomes available.

Recently, Thayer and Martin[29] have described a culture medium with selective properties which permits growth of the pathogenic *Neisseria gonorrhoeae* and *meningitidis* while greatly inhibiting or completely suppressing saprophytic *Neisseria* species like *sicca, catarrhalis* and others. The selective medium is prepared by adding 25 u./ml. of polymyxin B and 10 mcg./ml. of ristocetin to conventional media. Overgrowth of gonococcal colonies by bacterial contaminants encountered in cervical, vaginal and rectal specimens is almost totally prevented. The sometimes diagnostically confusing *Mima polymorpha* var. *oxidans* fails to grow. Thus, false positive cultural diagnosis of gonorrhea due to oxidase-positive *Mima* and saprophytic *Neisseria*, which were infrequently found in genitourinary specimens anyway, is almost wholly lacking. Therefore, presumptive testing (oxidase positive colonies of gram-negative diplococci) becomes a more acceptable diagnostic procedure particularly when large numbers of cultures must be examined by limited technical personnel. The clinician should find the medium helpful in "test of cure measures" for evaluating therapeutic drugs and drug regimens, especially of the patient who is known to have gonococcal proctitis.

At present, the selective medium is handicapped for rapid gonococcal identification in that most strains grow slowly during the first 24 hours, not reaching normal-sized colonies until incubated for 48 hours. If this difficulty can be overcome, it will be possible to inoculate a culture slant, incubate it for 24 hours and mail the culture to a central laboratory for identification by FA procedures, thus bypassing lengthy fermentation studies.

The selective medium should be of value in finding the incidence of gonorrheal proctitis in the female and the homosexual male.

In passing, it should be observed that *N. meningitidis* grows well on

Table 1. *Treatment Results of Uncomplicated Gonorrhea in Females Using Currently Recommended Antibiotic Therapy*

The following schedules were rotated weekly in participating clinics:	NUMBER COMPLETING TWO-WEEK FOLLOW-UP	PERCENTAGE COMPLETING TWO-WEEK FOLLOW-UP	NUMBER APPARENTLY CURED	PERCENTAGE APPARENTLY CURED
1. Procaine penicillin G in oil with 2% aluminum monostearate (PAM). Single IM injection—1,200,000 units.	227	70.7	145	63.9
2. Benzathine penicillin G. Single IM injection—1,200,000 units.	160	69.0	94	58.8
3. Aqueous procaine penicillin G. Single IM injection—1,200,000 units.	130	69.1	86	66.2
4. Combination schedule. One injection each of: PAM—600,000 units. Benzathine penicillin G—1,200,000 units.	149	66.8	82	55.0
5. PAB (preparation containing equal parts aqueous procaine and Benzathine penicillin G). Single IM injection—2,400,000 units.	170	68.5	112	65.9
6. Streptomycin. Single IM injection—1 gram.	197	70.4	108	54.8
7. Tetracycline phosphate—total 500 mg. Two IM injections of 250 mg at 24 hour intervals.	110	80.3	82	74.5
8. Chloramphenicol. Single IM injection—1 gram	157	73.4	108	68.8
9. Triacetyloleandomycin (oral)—total 3 grams. 500 mg. every 4 hours.	154	70.6	110	71.4
10. Tetracycline (with Amphotericin B) (oral)—total 3 grams. 500 mg. every 4 hours.	161	68.8	128	79.5

the Thayer-Martin selective medium and that bacteria for the pharyngeal region, including saprophytic *Neisseria* such as *catarrhalis, sicca* and others, are almost totally inhibited. Tests have shown[30] that many more asymptomatic meningococcal carriers are discovered by this method and in a much shorter time. Typing may be carried out usually with primary isolates without purification procedures.

If syphilis were eradicated tomorrow permitting diversion of case-finding personnel from this priority area, and we had an adequate serologic test for the identification of individuals with asymptomatic disease requiring treatment; if it were possible to apply speed zone epidemiology, currently recommended antibiotic treatment schedules and selective blood testing, it is doubtful that any significant reduction in gonorrhea morbidity would occur at this time. One apparent reason for this has been brought home to us in a recent cooperative clinical study in which ten antibiotic treatment schedules were evaluated in the treatment of the female gonorrhea patient. These schedules included the maximum treatments presently recommended for uncomplicated gonorrhea in women. Now with an average of 162 patients completing two-week follow-up on each of the ten schedules, failures are noted in 20 to 40 per cent of those treated[32] (see Table 1).

It should be mentioned that, while some failures in this study undoubtedly represent reinfections, two-week follow-up in the female is probably less than what is required to demonstrate cure, since it is recognized that the menses, unusual sexual excitement and other factors can cause the female to become at least intermittently infectious again.

A new treatment study designed to overcome this therapeutic deficit in women has just begun. The initial phase of the study is in progress now in a selected confined group of women in which heterosexual contact—and thus reinfection—is virtually impossible. A three-month follow-up period is being used to rule out late relapse in the closed study population.

TOMORROW

The future, in some respects, looks a good deal brighter than the past. The reason for such optimism is due to the recent finding of Kellogg et al.[12] from this laboratory that gonococci in culture can be maintained in the virulent form. Four morphologically distinct colonial types have been observed in culture. Type 1 is of most interest as it is found only in the purulent exudate from acute gonorrhea of the male. Other types appear when unselected subculturing of the primary isolate occurs and are probably due to the genetic instability of the type 1 cells *in vitro*. After 69 passages on suitable culture media, type 4 cells, typical of so-called "laboratory strains," were no longer virulent. It is with such cultures that experimental studies in serodiagnosis[18] and immunity[15] have been performed in the past. On the other hand, type 1 cells, after 69 selected subcultures, retained virulence and infected male volunteers, producing typical gonorrheal signs and symptoms.

The use of virulent cultures in experimental studies promises to advance our knowledge of gonorrhea over anything previously known and may make it possible to control the disease.

It is conceivable that study of antigenic fractions of the type 1 organism will lead to skin-testing antigens. Already, a protein fraction has been isolated for serologic precipitation reactions that have good specificity.[19] Such a test would be of great value in epidemiological surveys. Serologic grouping of gonococci may become possible and differences discovered in gonococci isolated from symptomatic and asymptomatic cases. Physiological and biochemical studies of the virulent organism may reveal metabolic pathways that will lead to better diagnostic media.

It will be possible under controlled conditions to study results of therapy in human volunteers using type 1 strains of known antibiotic sensitivity to infect the subjects. The interaction of serum antibiotic concentration, gonococcal susceptibility to antibiotic, excretion rate, etc., can be observed and related to failure to cure the disease.

The ultimate finding, of course, would be the discovery of an immunizing antigen for use in preventive vaccination. The finding and application of such an immunizing agent, together with specific therapy, would satisfy the basic tenets of communicable disease management and open the door to an adequate gonorrheal control program.

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Gonorrhea and Nonspecific Urethritis

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The gonococcus resembles the rat. Despite major efforts to eradicate it from our society by enlightened epidemiological control, modern diagnostic methods and new antibiotics, it has continued to flourish. In remarks made to the World Health Organization, Dr. Thorstein Guthe said that no method as yet has been found of "catching up with this heel-less Achilles."

INCIDENCE

It has been estimated that the incidence of gonorrhea in this country is over one and one-half million cases per year, 80 per cent of these being unreported.[3] A disturbing aspect of this is the steady increase of the gonorrhea rate in this and other countries. Of the 105 countries participating in the study by the World Health Organization, 71 per cent showed a rising trend in the disease rate. No figures are available on the incidence of nonspecific urethritis, a disease with comparable morbidity.

Contributing Factors

Various factors have been suggested as contributing to the dismal failure of our modern society to suppress or control gonorrhea.

1. *Public attitudes.* The general concept among the laity about gonorrhea is an indifferent one. It is thought by many to be a trifling affliction which can be cured by one visit to the drugstore, and which, in truth, is no worse than a bad cold. In the public health field, on the other hand, insurmountable problems in control of the disease have resulted in a defeatist attitude. Today nearly all funds for venereal disease control are earmarked for the eradication of syphilis, a disease which is easily detectable, and which responds predictably to treatment, and whose contacts are

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readily traceable. The admitted failure in the control of gonorrhea has lessened the interest of public health authorities in this area.

2. *The inability to diagnose gonorrhea in the female* is another formidable obstacle in the control of the disease. The lack of efficient diagnostic procedures, and the usual absence of symptoms in women, result in the female serving as a chronic reservoir of disease. Ordinary smears and cultures are usually valueless, and the recently developed fluorescent antibody technique has at least a 20 per cent incidence of false negative results.

3. An obvious reason for the increase in gonorrhea lies in *the emergence of antibiotic-resistant strains.* As time progresses, we might expect that penicillin and broad-spectrum resistant gonococci will multiply and disseminate more rapidly than the tractable strains.

4. *The treatment of gonorrhea by unqualified personnel* sharply decreases the chances of its control. A patient treated by a druggist has no laboratory confirmation of the diagnosis or cure, while the pharmacist himself has no interest in, or responsibility for, the identification and treatment of the contact. Years ago, the physician treated all cases of urethritis; today the vast majority of his patients represent penicillin-resistant cases, who come to him because self-treatment has failed.

5. *The extremely short incubation period* of the disease (three to seven days) makes it possible for gonorrhea to be spread more rapidly than contacts can be followed up and treated. This, together with the difficulty in diagnosis in the female, presents a formidable problem.

6. *Public health aspects of nonspecific urethritis.* Little is known of the epidemiology of nongonorrheal urethritis. This is because it is a convenient term for a number of various entities which may or may not be acquired through sexual exposure. It includes atypical cases of gonorrhea seen after treatment, as well as patients with Reiter's disease, abacterial pyuria, urethral stricture, chemical urethritis, trichomoniasis and chronic prostatitis.

Nonspecific urethral discharge is a symptom of a disease rather than a specific disease entity. The public attitude toward this disease has always been indifferent because it does not carry the social stigma which accompanies gonorrhea. In the armed forces, individuals suffering from nonspecific urethritis, and their organizational units, are not subject to the same disciplinary measures imposed when the urethritis is caused by the gonococcus, although transmission may be by the same sexual route. Nevertheless, nonspecific urethritis is often more difficult to treat than gonorrheal urethritis.

THE CLINICAL COURSE OF GONORRHEA

Signs and Symptoms. In the male, gonorrhea follows a typical course.

Three to seven days after exposure, a purulent discharge begins, which is diffuse, and accompanied by urethral edema. Treatment with antibiotics usually brings about prompt disappearance within 24 hours, unless the organism is resistant to the drug. In women, the disease may be completely without symptoms, although the cervix, vagina, Skene's and Bartholin's glands as well as the urethra are infected. Treatment, again, is with antibiotics, which should be continued until the gonococcal organisms cannot be demonstrated in the urethra, cervical canal or periurethral glands. Complications in women are more serious than in men, and include the whole gamut of pelvic inflammatory diseases. Throughout the entire course, diagnosis is difficult and demonstration of the gonococcus by laboratory methods is inconsistent. Fluorescent antibody examination of material taken from the urethra and cervix is the most reliable method of identification.

Diagnosis and Treatment. In the male, diagnosis is simple. A gram stain of the urethral discharge reveals large numbers of gram-negative intracellular diplococci. Cultures will show *Neisseria gonorrhoeae.* In women, the diagnosis is more difficult and must be obtained by examining the material from the urethra, periurethral glands and cervix with the fluorescent antibody technique. Even with this method many cases will be missed.

Male patients are immediately and dramatically cured, if the gonococcus is penicillin-sensitive, by a single injection of 1,200,000 units of penicillin intramuscularly. The discharge should stop in 24 hours and all subsequent examinations by culture or the fluorescent antibody technique will be negative. If the discharge does not stop, and the gonococci persist in it, another type of antibiotic should be tried. This includes most of the broad-spectrum antibiotics including tetracycline, oxytetracycline (Terramycin), chlortetracycline (Aureomycin), and chloramphenicol (Chloromycetin). The dosage should be high, employing 500 mg. every six hours for a total of five days. After a five-day rest period, if the discharge is still present, another type of antibiotic may be used for another five-day course.

Test for cure in the male is simple. After a month has passed without urethral discharge, and pus cells and bacteria are absent from the voided urine, the patient is cured. In women, the criterion for cure consists of multiple successive negative examinations for the gonococcus in the urethra and cervical canal by the fluorescent antibody technique.

Treatment of Antibiotic-Resistant Cases. No new or spectacular therapy is available for treatment of patients failing to respond to penicillin or the other antibiotics. Such patients must be followed carefully with courses of various antibiotics at weekly intervals, with frequent tests by culture and sensitivity studies to see if new organisms are present. Patients should receive the benefit of a hygienic regimen, with adequate periods of rest, exercise, freedom from sexual excitement and the interdiction of alcohol and spicy foods. However, the patient likely to get venereal disease frequently resists a hygienic regimen.

THE CLINICAL COURSE OF NONSPECIFIC URETHRITIS

Signs and Symptoms. The incubation period of nonspecific urethritis is not typical. Instead of a fixed incubation period of three to seven days, a nonspecific discharge may appear 24 hours to several months after exposure. There may or may not be a history of sexual contact. Many cases of nonspecific urethritis result from a metastatic prostatitis, infected by an upper respiratory infection.

The urethral discharge is usually mucoid and scanty rather than purulent and diffuse, and may only exist as a morning drop, which has accumulated during the night without urination.

Diagnosis. Diagnosis of nonspecific urethritis is made by microscopic examination of the urethral discharge. The absence of gram-negative intracellular diplococci by any of the three laboratory methods confirms the presence of nongonorrheal (nonspecific) urethritis. Various types of organisms, or none at all, may be found. The most common type of pyogens are staphylococci, coliform organisms, miscellaneous cocci and diphtheroids.

Treatment. Penicillin is of little value in the treatment of nonspecific urethritis. A culture of the urethral discharge with sensitivity studies should be made and treatment carried out with the appropriate antibiotic. This includes nearly all of the broad-spectrum group. Patients with nonspecific urethritis should also observe a health regimen similar to that advised in the treatment of gonorrhea, and avoid alcohol and highly seasoned foods. If the discharge persists over four weeks, complete urological studies should be carried out to determine the cause of the chronicity.

TRICHOMONAS VAGINALIS URETHRITIS

Signs and Symptoms. Patients with trichomoniasis may have no symptoms at all except a slight urethral discharge accompanied by itching and a mild dysuria. It is a chronic low grade infection which does not ordinarily respond to any type of antibiotic therapy.

Diagnosis. Diagnosis of this infestation is made by examination of the urethral discharge suspended in saline solution. A typical trichomonad, which is the size of a white blood cell, will be seen. This protozoan may be found in a wet suspension of prostatic fluid. If no urethral discharge is present, a centrifuged urine sediment, examined wet, may also reveal the organism.

Treatment. The drug metronidazole (Flagyl)[1] appears to be specific in destroying this protozoan. The dosage is 250 mg. given orally, twice daily for a period of one to two weeks. Since the source of the infection is in the marital partner, the wife as well as the husband should be treated with this medication. A high percentage of cure (85 per cent) has been reported by this method. It is probable that failure is due to reinfection or extramarital exposure.

REITER'S DISEASE

Signs and Symptoms. The triad of chronic urethritis associated with conjunctivitis and polymigratory arthritis has been well known ever since Reiter's original description in 1916. Little has been learned about it since then. The conjunctivitis may be followed by iritis and keratitis. The disease is accompanied by low grade fever, leukocytosis, and an increased sedimentation rate. Remissions and exacerbations may occur.

Diagnosis. Diagnosis is made by the typical history and findings of urethritis, conjunctivitis and arthritis. There are no specific diagnostic tests available. The finding of pleuropneumonia-like organisms ("PPLO") are probably of incidental significance only, as these bacteria are normal inhabitants of the urinary tract. It is probable that this disease is caused by a virus, as yet unidentified.

Treatment. There is no specific treatment. Instead, various courses of broad-spectrum antibiotics are given empirically and supportive and symptomatic treatment carried out.

TREATMENT OF THE CHRONIC URETHRAL DISCHARGE

Neither the patient nor the physician need be concerned about a nonspecific urethral discharge until it becomes chronic. After it has survived four weeks of therapy with various antibiotics, it may be classified as a urological problem and complete urological investigation made to determine the cause of its chronicity. The common causes of refractory urethritis, and their management follow:

1. *Urethral Stricture.* This is the most common cause of persistent urethral discharge. It is seen in patients who have had previous attacks of urethritis with inflammatory or iatrogenic strictures. The stricture is both diagnosed and treated by the *gentle* passage of a No. 24 to No. 26 F. steel sound through the urethra under local anesthesia and aseptic conditions. The discovery and periodic dilatation of this stricture will result in the prompt disappearance of the discharge.

2. *Overtreatment.* Since local therapy was virtually abandoned in favor of antibiotic therapy, overtreatment is infrequently seen. However, occasionally patients are observed who have been treated by frequent instillations of medications into the urethra, or by instrumentation. These maneuvers, instead of ablating the infection, may cause a traumatic or chemical form of urethritis, which keeps the discharge active.

3. *Balanoposthitis.* A long foreskin, associated with inflammatory changes, frequently causes a urethral discharge. If attempts at hygienic treatment are unsatisfactory, a circumcision should be carried out.

4. *Chronic Prostatitis.* This is a common cause of chronic urethritis. It is uncertain as to whether prostatic massage is of any benefit except as a diagnostic measure; i.e., to obtain prostatic fluid for examination, cell count and culture. The prostate gland may be emptied much more effica-

ciously by sexual intercourse, and this should be advised if the patient has refrained from intercourse due to interdiction by his physician. Culture and sensitivity studies of the prostatic fluid, with treatment by the appropriate antibiotic is indicated. Hot sitz baths also help.

5. *The Use of Alcohol.* Many patients develop a urethral discharge simply as a result of the overuse of alcohol with excretion of alcohol and its congeners in the urine. A period of strict teetotalism will cure such a urethritis.

6. *Recurrent Infection.* A patient who frequently exposes himself to his previous sexual contacts, or to new ones, will obviously suffer reinfection of the urethra. Surprisingly enough, the patient may not find it important enough to tell his physician about his new experiences.

7. *The Neurotic Patient.* Many patients keep a urethritis active by continually stripping the urethra to see if any discharge is present. The mechanical irritation resulting from this maneuver, if it is persisted in until mucus is expressed, is sufficient to keep a chronic urethritis going. Because of the high emotional investiture in the genital organs, there is a high incidence of psychic overlay in symptoms resulting from a mild urethral discharge. Such patients must have much reassurance that the urethritis will not affect their future health or fertility, and should be advised against stripping the urethra to see if discharge is present.

HOW MAY GONORRHEA BE CONTROLLED EFFECTIVELY?

The admitted failure of public health authorities to control gonorrhea has been mentioned. Many of them feel that all efforts will continue to be futile until a vaccine is found to cure the disease[4] or until a serologic test is developed to make immediate diagnosis possible.[2] Thus, the most formidable attack on the disease would result from the development of better diagnostic tools and improved medication. Research funds should be provided to medical centers to encourage the development of better diagnostic tests, particularly in the female, and to further bacteriological and clinical work in the production of new antibiotics and chemotherapeutic agents for treatment of the antibiotic-resistant strains of gonorrhea.

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The Gynecological Lesions of Lymphogranuloma Venereum and Granuloma Inguinale

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These two quite distinct diseases are often confused with each other. They have been given similar names, and also they often occur in the same areas, among the same sort of people, and sometimes even in the same patient. This account, based on observations made by our group in Jamaica, gives some of the present ideas about these conditions.

Lymphogranuloma venereum is caused by a virus. The diagnosis can be aided, though not completely confirmed, by the Frei intradermal skin test or the lymphogranuloma venereum complement fixation test. The former gives about 20 per cent false negative results, and the latter is often found to be positive in people who show no signs of the disease. Isolation of the virus from active lesions is conclusive, but difficult and expensive.

Granuloma inguinale is caused by a microbacillus called *Donovania granulomatis*. This has been isolated from the lesions, grown in culture, and subcultured; but so far the disease has never been produced in volunteers by infecting them with organisms from cultures, so Koch's postulates are not completely satisfied. The Donovan bodies can be seen, mainly in large mononuclear cells, in stained smears of diseased tissue. A complement fixation test is under trial.

The usual clinical features of the two diseases are compared in Table 1.

Lymphogranuloma venereum infections behave differently in the two sexes. Evanescent primary ulcers of the genitalia have been described in men, but we have never recognized them in women. Inguinal buboes are common in men; uncommon in women: but the reverse is true of rectal lesions. The reasons for these differences are obscure. The disease seems to be commoner, or at least to be recognized more often, in men than in

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Table 1. *Comparison of Clinical Features*

LYMPHOGRANULOMA VENEREUM	GRANULOMA INGUINALE
Primary ulcer (?)	Flat raised papule
Chronic ulceration with tissue destruction	Chronic granulomatous ulceration
Inguinal buboes (men > women)	Secondary inguinal adenitis
Proctocolitis and strictures (women > men)	Rectal ulcers (rare)
Soft swelling of labia/clitoris	Genital "elephantiasis"

women. In Jamaican clinics the number of new male cases is about four times the number of female cases (Douglas, 1962).

The skin lesions of granuloma inguinale tend to spread and coalesce, but seldom cause destruction of deep tissue unless there is heavy secondary infection. Secondary inguinal adenitis may be mistaken for true buboes. Rectal lesions are uncommon. Massive "elephantiasis" of the genitalia is a late manifestation. This disease is slightly more common in women than in men.

LYMPHOGRANULOMA VENEREUM

The usual manifestations of this disease in women are listed in Table 2.

Buboes, when they occur, seem to be an early phase of the infection. The incubation period is difficult to assess, but it is probably one to four weeks. Usually the patient complains of fever, headache, nausea and muscle pains. Lymph nodes both above and below the inguinal ligament become matted together, swollen and painful. They are firm and rubbery

Table 2. *Common Manifestations of Lymphogranuloma Venereum in Women*

Buboes (early, rare)

Vulvar Lesions
- Urethra – Stricture or loss
- Labia – Notching or fenestration: "Puffy swelling"
- Vagina – Stenosis
- Occasional secondary prolapse

Rectal Lesions
- Proctocolitis
- Stricture
- Fistula
- Distortion of sphincter

at first and later become fluctuant. The overlying skin turns a dusky purple and becomes adherent to the underlying mass, then breaks down into multiple sinuses. These heal slowly, leaving characteristic puckered linear scars. Recent buboes resolve quickly under treatment with sulfonamides or tetracycline. If they are fluctuant, the pus should be aspirated with a wide-bore needle introduced through healthy skin. This may prevent sinus formation.

Lesions of the vulva and vagina cause destruction of tissue, or dense fibrosis and stricture formation, or both. The process seems to begin with ulceration, often at the fourchette, on the labia minora, or beside the urethral meatus. There may be definite ulcers with a yellowish base, or merely red patches looking like abrasions of the skin with a little underlying edema. The ulcers are almost painless and are only slightly tender, so the patient may not notice them or may not think them worthy of consultation with a doctor (Fig. 1).

Insidiously, the ulcers progress to destroy underlying tissue. If they are on the labia, these become notched or fenestrated (Figs. 2 and 3). We think that "button-holed labia" are almost certain evidence of lymphogranuloma venereum. If the ulcers are at the urethra, this is gradually destroyed from below upward and so progressively shortened (Fig. 4). Control of urination is not lost unless the upper quarter-inch of the urethra

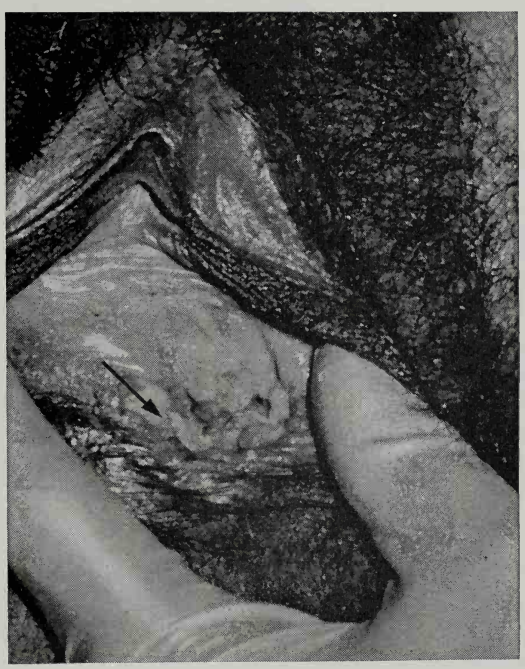

Figure 1. Early ulcer of lymphogranuloma venereum situated at the fourchette (see also Plate VI). It was painless and was discovered accidentally. (Stewart, D. B. in: Lymphogranuloma Venereum. Edited by M. M. Sigel, Univ. Miami Press, 1962.)

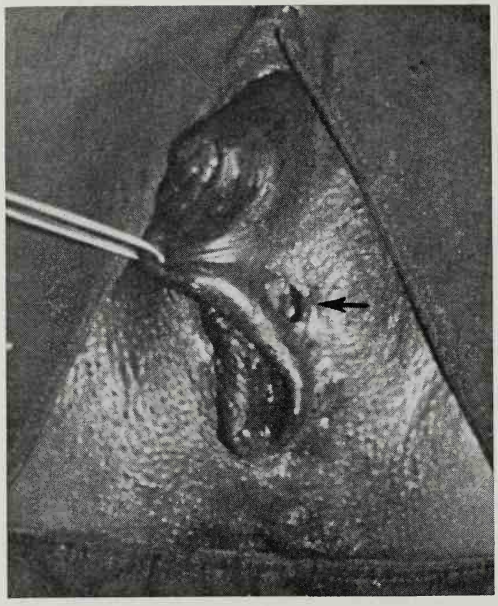

Figure 2. A punched-out early destructive ulcer of lymphogranuloma venereum on the labium minus.

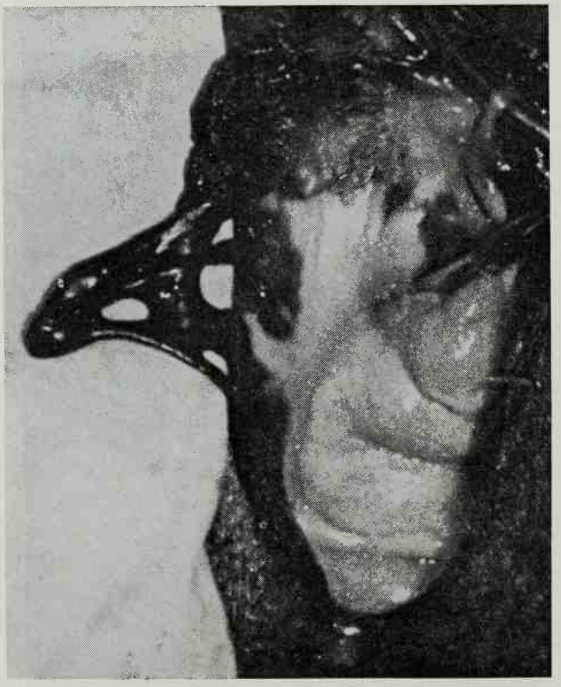

Figure 3. Multiple fenestration of the labium minus due to old lymphogranuloma venereum. The urethra was also destroyed.

is destroyed. Sometimes this part is spared but becomes fibrosed and narrowed, causing difficulty in micturition or even retention of urine. The opening of the bladder is found up behind the symphysis, where it may be distorted or concealed by tags of vaginal skin. Below this is a flat skin surface, perhaps with a few remaining tags to indicate where the urethra used to be (Fig. 5).

This process can be stopped by chemotherapy if it is detected in time, but if the whole urethra has been destroyed it is most difficult to restore continence. A new urethra can be constructed, but it is seldom possible to provide it with a competent sphincter. This is one of the most difficult problems in gynecological surgery.

Sometimes the vagina becomes fibrous and stenosed. Usually this begins at the vault: the cervix is concealed and the vagina is gradually shortened and obliterated. Occasionally the stenosis occurs near the introitus, and we have seen a multipara whose lower vagina closed completely over a period of less than four months, producing cryptomenorrhea (Fig. 6).

In some cases there is moderate soft swelling of the labia or clitoris. This is haphazard in its distribution and does not appear to be related to lymphatic obstruction. Massive hypertrophy with ulceration, the so-called "esthioméne," has been described as a characteristic of lymphogranuloma venereum. We do not think this is so.

Rectal lesions may occur alone or may be associated with lesions of the vulva, but for some reason they rarely occur in patients with buboes. The process begins as an acute purulent proctocolitis. The patient com-

Figure 4. Partial destruction of the urethra due to lymphogranuloma venereum (see also Plate VI). The site of the external urethral meatus is at (A), and the opening of the remaining upper part of the urethra at (B). The patient was still continent of urine. (Stewart, D. B. in: Lymphogranuloma Venereum. Edited by M. M. Sigel, Univ. Miami Press, 1962.)

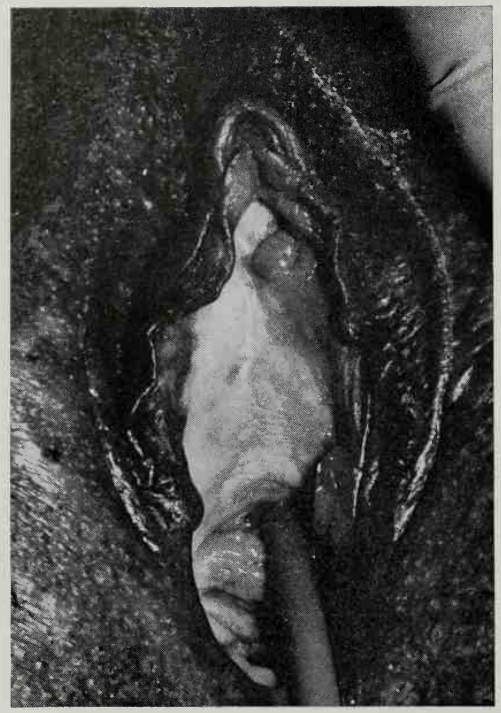

Figure 5. Complete destruction of the urethra. The catheter shows the hole in the bladder base. (Lawson and Stewart: Obstetrics and Gynaecology in the Tropics. In Press.)

Figure 6. Stenosis of the vagina and partial destruction of the urethra due to lymphogranuloma venereum. The probe points to the obliterated vagina; the arrow indicates the scarred opening of the remaining portion of the urethra. (Stewart, D. B.: Lymphogranuloma Venereum. Edited by M. M. Sigel, Univ. Miami Press, 1962.).

plains of passing blood, mucus and pus; there is tenesmus, alternating constipation and diarrhea, rectal pain, pyrexia and weight loss. Edematous perianal tags are often found (Fig. 7). The mucosa of the anal canal and rectum is rough and granular and the wall of the affected gut is thick and rigid. Characteristically these changes are usually most severe about 5 cm. from the anal margin, but they may extend as high as the pelvic colon.

Early treatment is important, as only about one-tenth of adequately treated cases develop strictures. It consists of rest and low residue diet plus tetracycline or streptomycin, which seem more effective than sulfonamides. It is not known whether improvement results from control of the virus or of the secondary bacterial infection.

Rectal strictures may develop within a few months after the initial proctocolitis, but sometimes not for several years. The most common symptom is increasing constipation and the passage of thin pencil-like stools with mucus, blood and pus. The stricture may be annular or tubelike, and there may be several strictures with relatively normal bowel between. The lowest edge of the stricture is usually about 4 or 5 cm. from the anal margin. Repeated straining at stool may result in uterovaginal prolapse (Fig. 8).

Distortion and incompetence of the anal sphincter is often associated with rectal stricture. It is not known whether this is caused directly by infection and fibrosis of the muscle or indirectly by interference with its

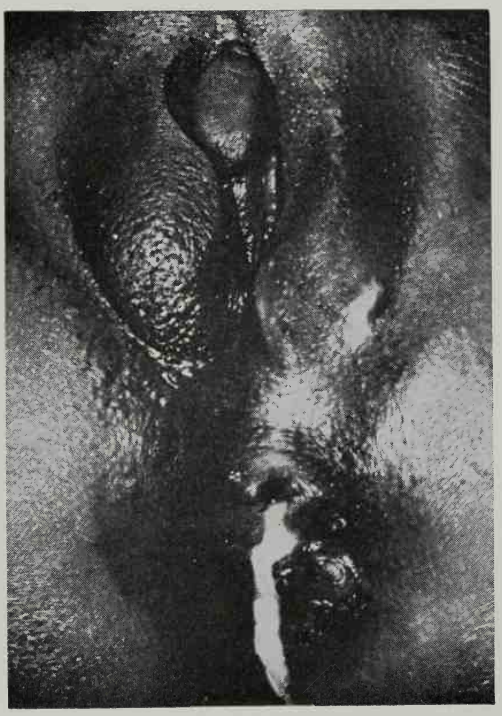

Figure 7. Acute proctocolitis, with pus pouring through the distorted and incompetent anal sphincter. The patient was a virgin aged 17. (Lawson and Stewart: Obstetrics and Gynaecology in the Tropics. In Press.)

nerve supply. Patients with this condition cannot control the escape of feces which pass through the stricture. Rarely, the perianal tissues become honeycombed with abscesses and multiple sinuses opening in the lumen and on the perineum.

About one-third of women with rectal strictures also have rectovaginal fistulas. The fistula is almost always in the midline, distal to the stricture, and about 3 or 4 cm. above the fourchette. Fistulas usually become smaller following chemotherapy, and occasionally they close spontaneously. Surgical closure seldom succeeds unless the rectal infection is cured first.

There has been much argument about how the rectum becomes infected. Many of the male patients with rectal lymphogranuloma are passive homosexuals, and a few women also probably are infected during anal coitus. We think, however, that in most cases the infection begins at the fourchette or in the lower vagina and spreads along tissue planes of the perineal body to invade the rectum where the fascia is thinnest and the vagina and rectum are closest to each other. This is the area where proctitis usually begins and the level above which strictures form and at which rectovaginal fistulas develop (Fig. 9).

It is difficult to say how prevalent this disease is. Grant and associates[1] have shown that over 40 per cent of Jamaican working-class people have a positive lymphogranuloma venereum complement fixation test, but this might be due to exposure to a related but harmless virus, or to subclinical lymphogranuloma infection of short duration, or to persistent but latent disease. A study among children shows that over 5 per cent develop a positive titer about the age of puberty, which may be a result of sexual

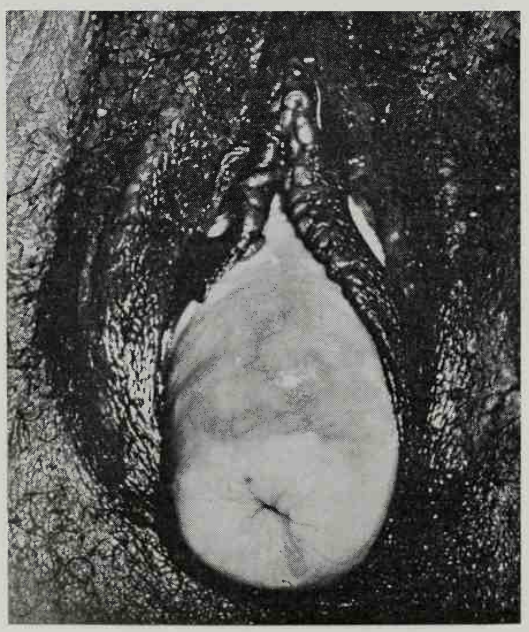

Figure 8. Prolapse in a nullipara due to severe rectal stricture. Note fenestration of labia minora. The patient also had complete destruction of the urethra and a rectovaginal fistula. (D. B. Stewart in: Lymphogranuloma Venereum. Edited by M. M. Sigel, Univ. Miami Press, 1962.)

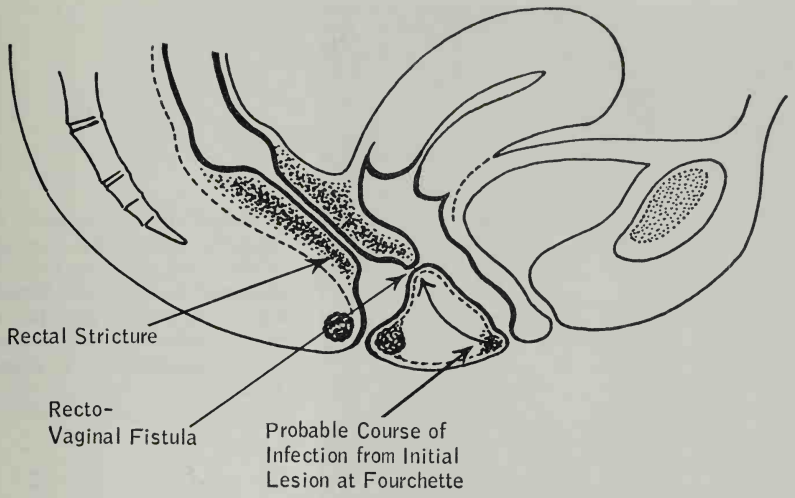

Figure 9. Diagram showing the typical relationship of a rectovaginal fistula to a rectal stricture. The infection probably reaches the rectovaginal septum from a primary lesion at the fourchette.

contacts. On the other hand, we have had young patients with lymphogranuloma who were undoubted virgins (e.g., the patient in Fig. 7) and admitted no history of sexual molestation, so the infection is probably not always venereal.

GRANULOMA INGUINALE (DONOVANOSIS)

This is primarily a disease of the skin and mucous membranes. There is no great difference between the sexes in its incidence or in its manifestations (Table 3). The earliest lesions are slightly raised flat-topped papules which subsequently ulcerate. They may appear anywhere on or near the external genitalia or in the vagina. The ulcers are usually irregular in shape with an uneven edge which may be bordered by papular lesions which have not yet broken down, or may be thickened and rolled (Fig. 10). The base

Table 3. *Common Manifestations of Granuloma Inguinale in Women*

Papules	
Ulcers	— Vulva Perineum Groins
Granulomas	— Cervix Vagina
Intrapelvic Thickening and Fibrosis	
Rare Extragenital Lesions	

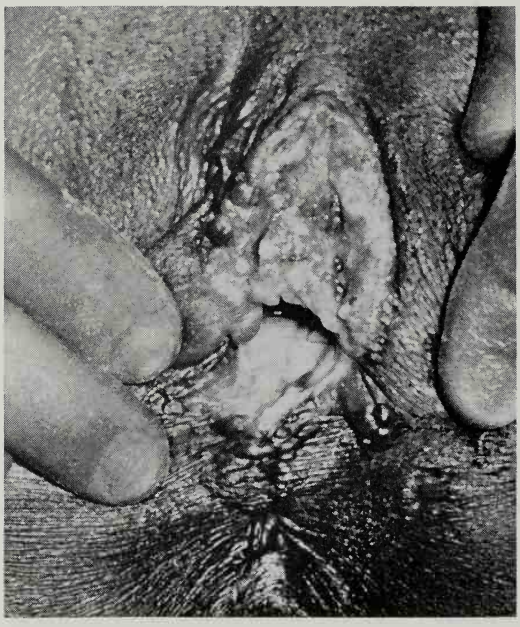

Figure 10. Untreated donovanosis (granuloma inguinale) of the vulva (see also Plate VI). Lesions like this are often mistaken for carcinoma. (Lawson and Stewart: Obstetrics and Gynaecology in the Tropics. In Press.)

of the ulcer is a dark-red beefy sheet of granulation tissue which sometimes shows a cobblestone pattern. This may be covered with slough if there is much secondary infection. The vulvar ulcers are often mistaken for carcinoma. Lesions on the cervix or vaginal vault appear as proliferating red masses of granulation tissue which may also be mistaken for carcinoma. Frequently these vaginal or cervical lesions are associated with a curiously uniform, rubbery thickening of the paracervical tissues extending out to the side wall of the pelvis, usually on one side only. We have seen such a mass gradually become so dense and fibrous that it completely occluded a ureter.

Extragenital lesions are sometimes found—usually in the mouth, nose or pharynx—in patients who also have genital lesions. We have seen one case of proven donovanosis of the rectum and rectovaginal septum.

There is seldom much destruction of tissue, as there is in lymphogranuloma venereum, but quite massive swelling or "elephantiasis" may develop either while the ulcers are still active (Fig. 11), or after they have healed (Fig. 12). The cause of this is obscure; the lymphatics are widely dilated but they do not seem to be obstructed, since dye injected into the tissue rapidly reaches the regional lymph nodes.

When the ulcers heal they leave a characteristic smooth, pliable, depigmented skin surface (Fig. 12).

The definite diagnosis of granuloma inguinale depends on seeing the Donovan bodies in tissue smears stained with Giemsa's solution. Usually they are encapsulated and clustered in the cytoplasm of large mononuclear cells. Even in an active case they are difficult to find. We have seldom

Figure 11. Active donovanosis with hypertrophy of the labia (see also Plate VI). (D. B. Stewart in Lymphogranuloma Venereum. Edited by M. M. Sigel, Univ. Miami Press, 1962.)

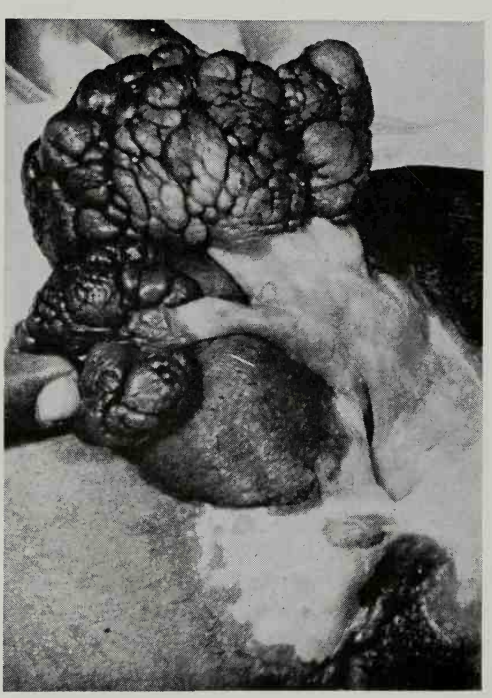

Figure 12. Hypertrophy of the labia which developed after treatment of donovanosis. Note depigmented scar. (Lawson and Stewart: Obstetrics and Gynaecology in the Tropics. In Press.)

been able to demonstrate them in histological sections, either by hematoxylin and eosin or silver stains. The histological picture of an active ulcer of granuloma inguinale is sometimes characteristic enough to warrant a provisional diagnosis. Very often in practice the clinical diagnosis is confirmed by a therapeutic test; if the ulcers heal rapidly with intensive streptomycin treatment they can be assumed to have been due to granuloma inguinale. We usually give 40 gm. of streptomycin over a period of 20 days. However, tetracycline is a safer drug to use, since the heavy dosage of streptomycin may cause vestibular disturbances.

COMPARATIVE HISTOLOGY

The appearance of the ulcers and their main histological features are shown in Table 4.

Table 4. *Appearance of the Ulcers and Their Main Histologic Features*

LYMPHOGRANULOMA VENEREUM	GRANULOMA INGUINALE
Ulcers	
Chronic	Rolled edge
Destructive	Red base
Painless	Painful
Histology	
Chronic appearance	*Subacute* appearance
Fibrosis	Pseudo-epitheliomatous
Round cells	Micro-abscesses
Giant cells	Dense exudate
Possibly premalignant	Probably premalignant

The most interesting point about the ulcers of lymphogranuloma venereum is that even quite recent ones are interpreted by the pathologist as showing a very chronic type of inflammatory reaction, with much deposition of collagenous scar tissue interspersed with collections of plasma cells, lymphocytes and occasional giant cells. This appearance is difficult to reconcile with the tissue destruction which these ulcers produce. Possibly there is some interference with the local nerve supply, which could account for the painlessness of the ulcers and also for a trophic type of tissue destruction, though this is pure speculation.

The ulcers of granuloma inguinale show a more subacute type of inflammation. The epithelium at the margin often shows marked acanthosis and a pseudo-epitheliomatous appearance. The granulation tissue of the

Fig. 1. Early ulcer of lymphogranuloma venereum situated at the fourchette. It was painless and was discovered accidentally.

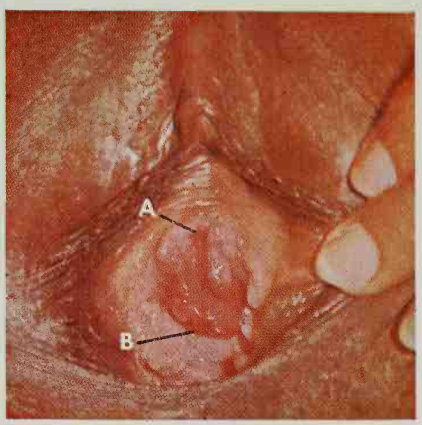

Fig. 4. Partial destruction of the urethra due to lymphogranuloma venereum. The site of the external urethral meatus is at A, and the opening of the remaining upper part of the urethra at B. The patient was still continent of urine.

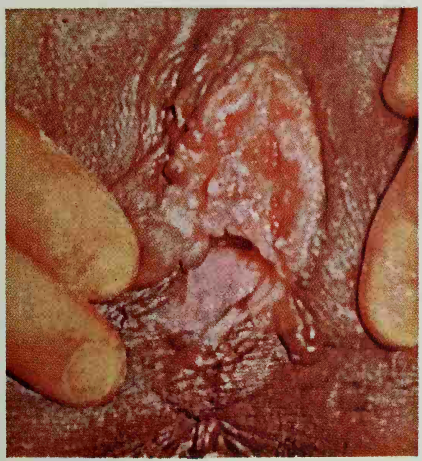

Fig. 10. Untreated donovanosis (granuloma inguinale) of the vulva. Lesions like this are often mistaken for carcinoma.

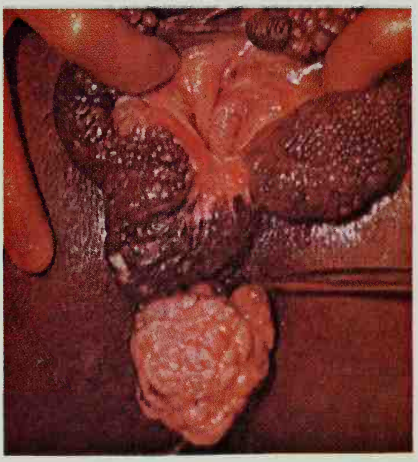

Fig. 11. Active donovanosis with hypertrophy of the labia.

base is densely infiltrated with chronic inflammatory cells and scattered macrophages. Many small collections of polymorphonuclear leukocytes (micro-abscesses) are present. The capillaries are prominent because the cells which form their walls are thickened.

These appearances have been described in more detail and illustrated elsewhere.[1, 3]

RELATION TO CARCINOMA

A relationship between lymphogranuloma venereum and cancer is not convincing. We have seen three patients who developed, respectively, carcinoma of the urethra, of the rectum and of the anus late in the course of this disease, but this might just be coincidental.

However, we have no doubt that granuloma inguinale is premalignant. Carcinoma of the vulva and carcinoma of the penis are both common in Jamaica among young people, and a considerable proportion of these patients give a history of having had earlier lesions which were characteristic of granuloma inguinale and which healed with antibiotic treatment only to break down again as proven carcinoma. Granuloma inguinale and carcinoma have been found together in the same genital lesions in both male and female patients (Fig. 13). The association is not unexpected in view of the marked epithelial unrest which is characteristic of the margins

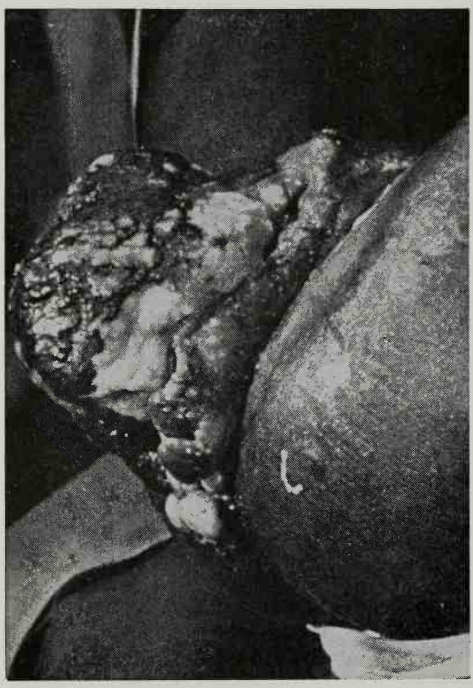

Figure 13. Carcinoma of the vulva superimposed on hypertrophy due to untreated donovanosis.

of the ulcers. This is a relationship which merits further research, but unfortunately no experimental animal seems to be susceptible to granuloma inguinale, and—probably fortunately—the number of human cases of the disease seems to be diminishing. Nevertheless it should be investigated as a possible addition to our understanding of carcinogenesis.

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The Nonvenereal Diseases of the Genitals

Their Differentiation from Venereal Lesions

JOHN F. WILSON, M.D., M.S.*

Syphilis has been designated the great imitator because it can mimic so many diseases. It would be impossible even to tabulate a complete list of such diseases and even more impossible to discuss in detail their differential diagnoses. However, a constant awareness of syphilis on the part of the physician is of greatest value in coming to an accurate diagnosis of the disease.

It has been aptly stated that in order to know what is "venereal" for diagnostic purposes, one must first be able to recognize that which is "not venereal." While syphilis may mimic many diseases, careful attention to fine details of morphologic change existing on the skin make clinical recognition possible and in some instances even essential, as in those cases in which laboratory studies are equivocal.

The anogenital region, because of its location and the changes which the skin undergoes in this area, requires special consideration. As most of the changes on the cutaneous surface in syphilis tend to be located in the genital region, it seems imperative to direct greatest attention to the differential diagnosis of those lesions occurring in this area. Also, in view of the great increase in homosexual practices in society at the present time, especially in larger cities, it seems advisable to include affections of the anal region in the differential diagnosis of venereal diseases.

Moisture and friction produce secondary changes in the anogenital areas which tend to obscure the true diagnosis. Intertrigo, folliculitis, edema, maceration and even fissuring of the skin produce secondary inflammatory changes which, when superimposed upon the original morphologic picture of disease, tend to make more difficult the accurate classification of diseases occurring in this area. Itching when present—and it is common because of the inflammation in the area—adds the secondary changes of excoriation and lichenification, producing a more confusing picture to confound the diagnostician. It is therefore of the greatest impor-

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tance that such secondary changes be treated first by mild soothing applications so that a diagnosis can then properly be made.

A listing of the various diseases affecting the anogenital region, slightly modified from its original source,* follows:

I. PYOGENIC DISEASES

a. Impetigo
b. Pyoderma
c. Ecthyma
d. Folliculitis
e. Furunculosis
f. Carbuncle
g. Erysipelas
h. Pyogenic granuloma
i. Hidradenitis suppurativa

II. DERMATOMYCOSES

a. Superficial
   Tinea cruris
   Erythrasma
   Tinea versicolor
   Favus
   Moniliasis
b. Deep
   Blastomycosis
   Coccidioidomycosis
   Actinomycosis
   Sporotrichosis

III. ANIMAL PARASITES

a. Pediculosis pubis
b. Scabies

IV. FILTERABLE VIRUSES

a. Verruca vulgaris
b. Condyloma acuminatum
c. Molluscum contagiosum
d. Herpes simplex
e. Herpes zoster
f. Vaccinia

V. APHTHOSIS, ECTODERMOSIS EROSIVA PLURIORIFICIALIS and STEVENS-JOHNSON SYNDROME

a. Erythema multiforme
b. Behcet's syndrome

VI. NEURODERMATITIS

a. Disseminated neurodermatitis
b. Localized neurodermatitis
c. Pruritus ani
d. Pruritus vulvae
e. Pruritus of the penis and scrotum

VII. UNCLASSIFIED

a. Eczematous dermatitis
b. Intertrigo
c. Seborrheic dermatitis
d. Sulzberger-Garbe syndrome
e. Acne
f. Edema of the genitals
g. Urticaria
h. Psoriasis
i. Lichen planus
j. Porokeratosis
k. Lichen nitidus
l. Pemphigus
m. Hailey-Hailey disease
n. Xanthomatosis
o. Scleroderma
p. Cornu cutaneum
q. Fox-Fordyce disease
r. Lupus erythematosus
s. Hemorrhagic diseases
t. Leukemic diseases
u. Pseudolues papulosa
v. Acanthosis nigricans

* Callomon, Fritz T. and Wilson, John F.: The Nonvenereal Diseases of the Genitals: Etiology, Differential Diagnosis and Therapy. Springfield, Illinois, Charles C Thomas Company, 1956.

VIII. DRUG ERUPTIONS
- a. Localized
- b. Fixed
- c. Anaphylactic reactions

IX. PIGMENTARY CHANGES
- a. Hyperpigmentation
- b. Depigmentation

X. CHANGES OF THE PUBIC AND GENITAL HAIR

XI. NUTRITIONAL DEFICIENCIES

XII. GENITAL ULCERS
- a. Mechanical, thermal, chemical or physical trauma
- b. Nonvenereal infections
- c. Acute infectious diseases

XIII. DIFFUSE IRRITATIVE INFLAMMATION OF THE GLANS AND PREPUCE AND OF THE VULVA
- a. Common balanitis and balanoposthitis
- b. Diabetic balanoposthitis and vulvitis
- c. Inflammatory phimosis

XIV. PROGRESSIVE SCLEROTIC ATROPHIC PROCESSES OF THE PENIS AND VULVA
- a. Balanitis xerotica obliterans
- b. Lichen sclerosus et atrophicans
- c. Leukoplakia penis
- d. Leukoplakia vulvae

XV. NEOPLASMS
- a. Benign
- b. Malignant

XVI. LYMPHATIC SYSTEM DISEASES
- a. The nonvenereal bubo
- b. Elephantiasis lymphangiectatica
- c. Ulcus chronicum vulvae elephantiasticum

Such a list demonstrates that almost any disease of the integumentary system may appear in the genital region and with it occurs all of the confusing distortions attendant upon the regional changes of anatomical and physical peculiarities in this area.

No attempt could possibly be made in this short treatise to expound in detail upon all of these conditions but a number of them, some common, others uncommon, are presented by means of photographs and short case histories, to illustrate the difficult problems of the individual case and the details of differential diagnosis. As a further aid to diagnosis, 12 of the 20 black and white photographs are repeated in color.

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Figure 1 (see also Plate VII)

HERPES PROGENITALIS vs. SYPHILITIC CHANCRE

A white man, aged 49, presents an erosion of the penile meatus of 7 days' duration (Fig. 1). It is accompanied by slightly tender left inguinal lymphadenopathy. There is a history of intercourse with a prostitute about a month ago. There is no history of previous lesions in this same area. He occasionally develops herpes simplex on the lips after exposure to sunshine.

Darkfield examinations on 3 consecutive days were found negative. Serologic tests for syphilis were negative.

The lesion disappeared in about 7 days with the use of an ointment containing equal parts of glycerin and a hydrophilic ointment base (carefully avoiding the use of an antibiotic which might obscure the diagnosis, if further complications arose).

Note edema and erosion of the meatus.

Figure 2 (see also Plate VII)

MULTIPLE HERPES PROGENITALIS vs. MULTIPLE CHANCRES

A white man, aged 36, shows three superficial eroded lesions of the penis, one on the left side of the corona, the other two on the left side of the prepuce (Fig. 2). The superior one of the latter forms a "kissing" contact with the lesion on the corona. Duration—4 days. There is no evidence of regional lymphadenopathy. Careful questioning discloses a history of one previous attack in the same area 4 months ago. No history of suspicious intercourse.

Smears were negative for *Hemophilus ducreyi*. The darkfield examinations and serologic studies on the blood were found negative.

The lesions healed uneventfully. The patient has not had another attack in the past year.

Figure 3

PENILE HERPES ZOSTER vs. SYPHILITIC CHANCRE

A white man, aged 66, has an ulcerated, black crusted lesion of the right side of the penis of 1 week's duration (Fig. 3). There is a red halo of inflammation surrounding it. The appearance of the ulcer was preceded for 2 days by sharp pain radiating over the right flank and extending down the penis. There is tender, right-sided inguinal lymphadenopathy. Further examination disclosed an area of crusted, ruptured and some unbroken vesicles on the pubic region at the base of the penis and extending around the right side of the lower portion of the abdomen from the mid-back region.

Pain was characteristic of herpes zoster in this case but in occasional instances it may not occur until several days after the eruption appears or it may even be slight or absent.

This is an example of the importance of examining the entire surface of the skin.

Fig. 1. Herpes progenitalis vs. syphilitic chancre.

Fig. 2. Multiple herpes progenitalis vs. multiple chancres.

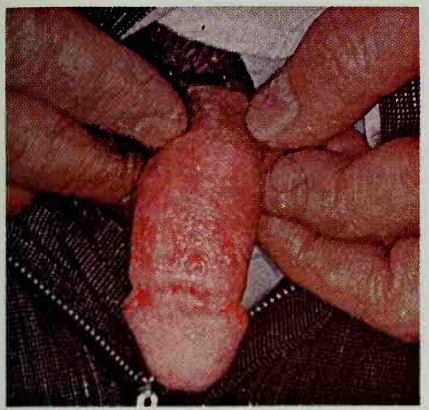

Fig. 6. Acute simple balanitis vs. syphilitic chancre.

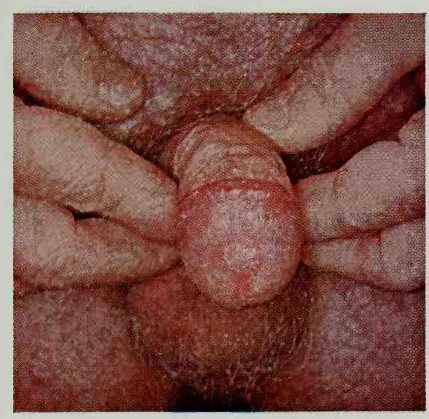

Fig. 7. Psoriasis vs. secondary syphilis.

Fig. 8. Erythema multiforme vs. syphilitic chancre.

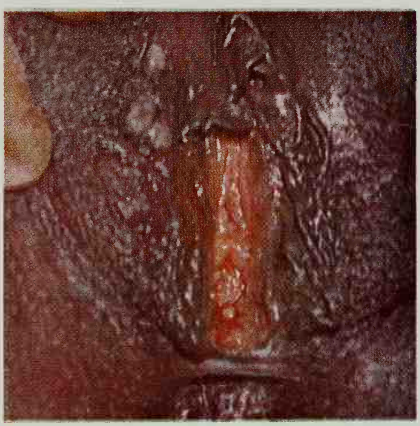

Fig. 10. Pyoderma vs. early syphilis.

Note: See text for Case Histories.

Figure 4

MONILIASIS WITH ULCERATION AND ACUTE EROSIVE BALANITIS vs. SYPHILITIC CHANCRE

A white man, aged, 48, has a crusted ulcer of the shaft of the penis and redness, oozing and edema of the prepuce and corona of 2 weeks' duration (Fig. 4). The ulcer is soft and superficial, the balanitis is acute and oozing with involvement of the entire prepuce adjacent to the corona.

Darkfield examination was negative on 3 successive days. Serologic tests for syphilis were negative. Smears for *Hemophilus ducreyi* were negative. *Candida albicans* was cultured from both areas on Pagano medium.

Both lesions healed in about a week with a simple drying lotion.

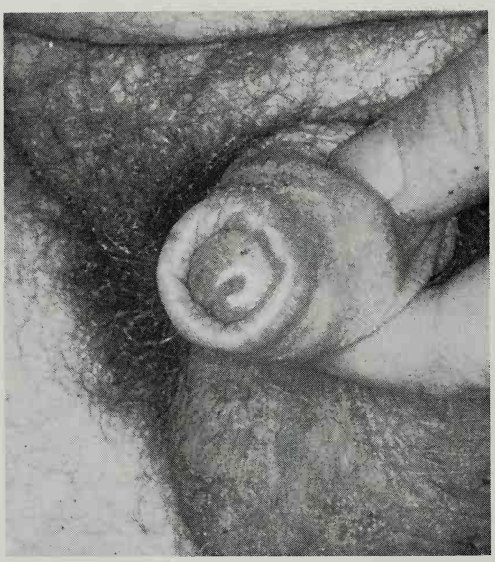

Figure 5

BALANOPOSTHITIS IN A DIABETIC vs. PHIMOTIC CHANCRE OF REDUNDANT PREPUCE

A white man, aged 58, has burning, redness and swelling of the distal portion of the penis of 3 weeks' duration (Fig. 5). He is an alcoholic who is also a diabetic, is obese and negligent with his diet. Retraction of the prepuce disclosed no evidence of chancre or other ulceration or erosion of the surface. Complete visualization by retraction is essential for accurate diagnosis.

The patient responded to treatment with simple drying lotions and improvement of his diabetes.

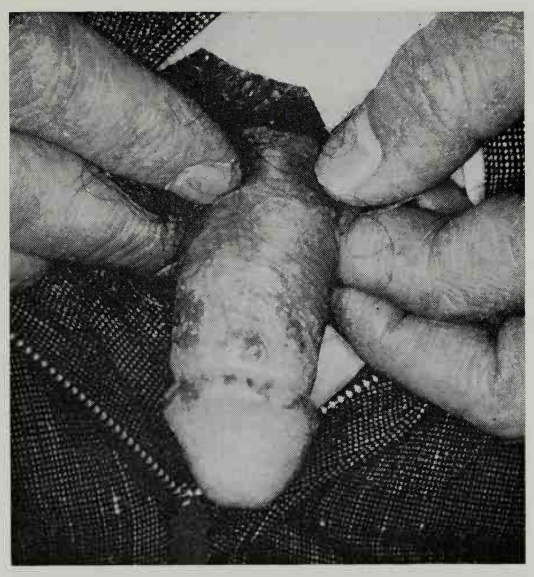

Figure 6 (see also Plate VII)

ACUTE SIMPLE BALANITIS vs. SYPHILITIC CHANCRE

This lesion (Fig. 6) occurred in a white man, aged 49, following extramarital exposure. These are superficial erosions without infiltration and are multiple rather than single. They have appeared 2 days after extramarital intercourse. There is tenderness of the entire area. The regional lymph nodes are not affected. It was felt that the diagnosis of syphilis could be excluded on the clinical findings but in view of the questionable exposure, the patient was kept under surveilance and the diagnosis of syphilis was later excluded.

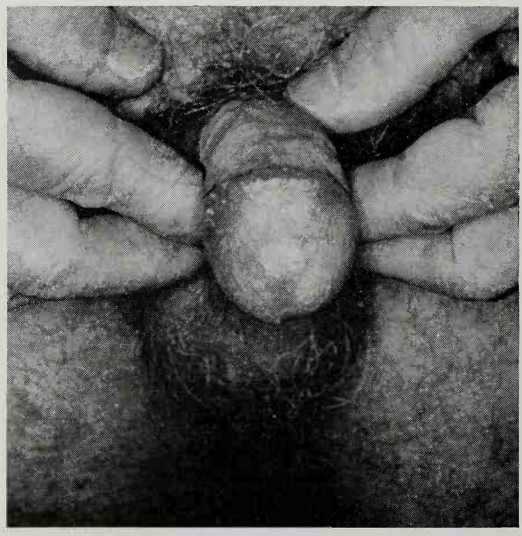

Figure 7 (see also Plate VII)

PSORIASIS vs. SECONDARY SYPHILIS

The patient, aged 54, has had a papulosquamous eruption of the glans penis especially at the corona for the past several weeks (Fig. 7.) The scales on the surface are grayish, there is very little inflammatory reaction. The patient has a history of an eruption of the elbows and knees of 5 years' duration, readily recognized as psoriasis vulgaris. It is felt that the lack of erosion and infiltration, plus the rather typical fine mica-like scale and the evidence of pin-point bleeding, characteristic of psoriasis, were sufficient to exclude syphilis.

The location of the lesions in these areas points to the importance of Köbner's phenomenon (friction and pressure in psoriasis) in coitus.

Figure 8 (see also Plate VII)

ERYTHEMA MULTIFORME vs. SYPHILITIC CHANCRE

A white man, aged 35, developed this superficially eroded penile lesion affecting the glans 4 days ago (Fig. 8). There is a similar eroded lesion of the lower lip at the center. Careful examination of the hands and wrists shows the beginning appearance of "iris" lesions of erythema multiforme. Further observations showed the classic picture of erythema multiforme.

Always examine the entire skin surface.

Figure 9

PYOGENIC GRANULOMA vs. SYPHILITIC CONDYLOMA

A white man, aged 56, has had a "wart" of the area of the penile meatus which has gradually enlarged in size during the past year (Fig. 9). It is dry and shows no evidence of inflammatory reaction. It is not painful and the regional lymph nodes, while shotty, are not enlarged.

The lesion was excised and showed pyogenic granuloma. Microscopic examination of the tissue is essential for the recognition of tumorous lesions. It could have been a cancerous lesion as well.

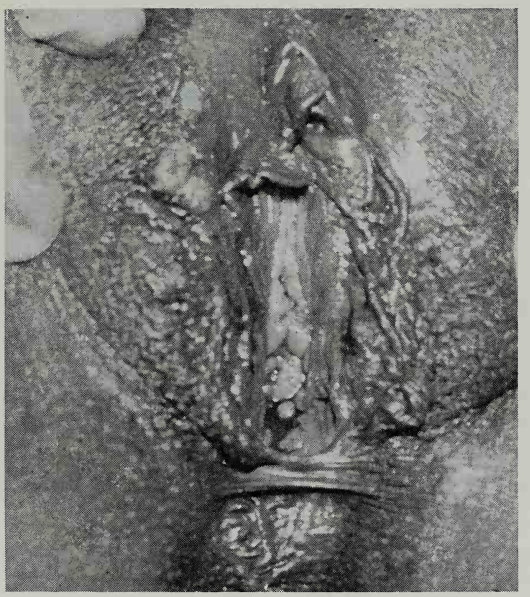

Figure 10 (See also Plate VII)

PYODERMA vs. EARLY SYPHILIS

A Negro woman, aged 27, was found to have eroded papules on the right labia majora at 10 to 11 o'clock in the above figure. Darkfield examination and serologic tests for syphilis were found to be negative. The surfaces of the lesions were eroded. There was a grayish, thin membrane and the lesions were not infiltrated. Beta hemolytic streptococci were isolated from the lesions. They disappeared in a few days with treatment, using a topical antibiotic (neomycin) ointment.

Figure 11

PEDICULOSIS PUBIS

While not truly venereal in origin, the nits and lice of pediculosis pubis are not infrequently found to be spread during intercourse. This case (Fig. 11) occurred in a white man, aged 59, who had severe itching with an eczematous eruption of his lower abdomen and upper, inner thighs for the past 7 days, following several days after intercourse with a prostitute. Antiparasitic medications produced prompt relief.

In this instance this was proved to be the only disease contracted by the patient.

Note the tiny nits on the hair shafts and also the larger dark areas of pediculi on the skin, under the hair.

Fig. 12. Squamous cell epithelioma of vulva vs. condyloma latum.

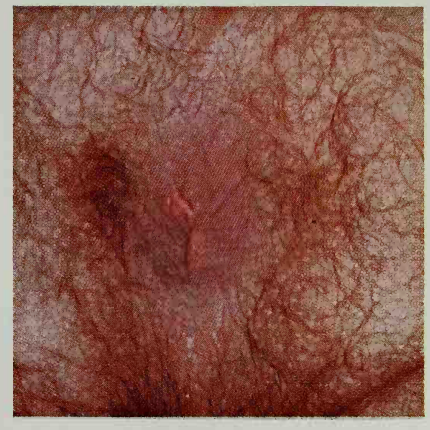

Fig. 15. Molluscum contagiosum, anal vs. condylomata lata.

Fig. 17. Leukoplakia vs. mucous patches.

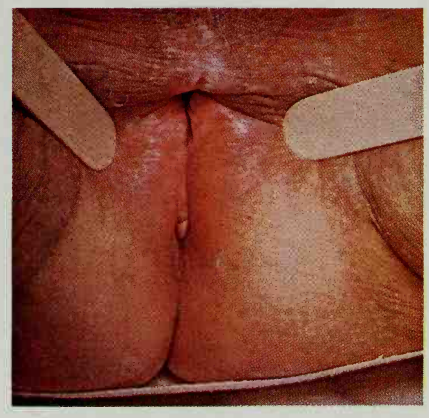

Fig. 18. Localized neurodermatitis vs. leukoplakia vs. mucous patches.

Fig. 19. Lichen sclerosus et atrophicans vs. mucous patches.

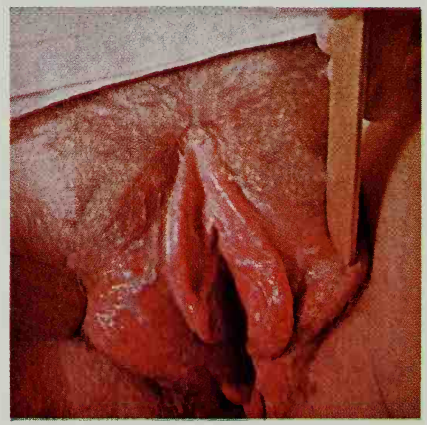

Fig. 20. Acute vulvitis (Trichomonas vaginalis vs. gonorrhea).

Note: See text for Case Histories.

Figure 12 (see also Plate VIII)

SQUAMOUS CELL EPITHELIOMA OF VULVA vs. CONDYLOMA LATUM

Such a far advanced lesion as demonstrated above with firm consistency and ulceration at the surface, came as a result of the epithelioma. A long history of gradual enlargement in size during the last year left little doubt of the diagnosis of carcinoma. Microscopic examinations of this tissue disclosed it to be of Grade 3 type.

Bilateral firm painless inguinal lymphadenopathy is a result of regional metastasis. This is an example of the problem of delayed diagnosis in the management of cancer in this area. It is a common problem and histories of 1 and 2 years' duration are not unusual.

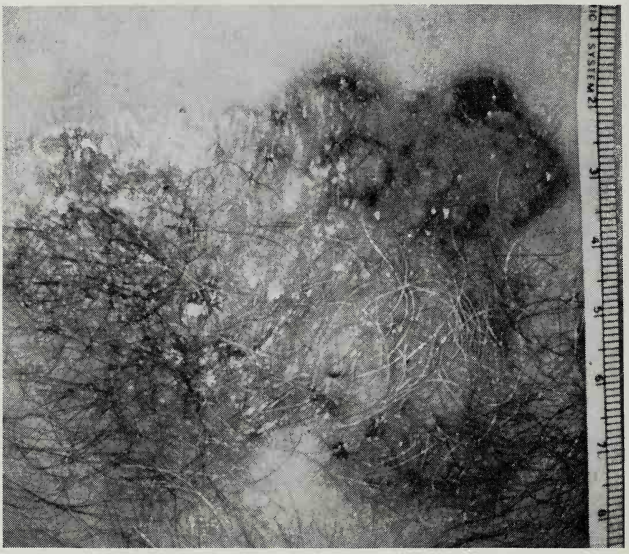

Figure 13

CICATRICIAL SUPERFICIAL BASAL CELL EPITHELIOMA vs. TERTIARY SYPHILIS, GUMMA

A white woman, aged 71, presents an ulcerated, crusted and scarred lesion of the pubic region of 4 years' duration (Fig. 13). There is a marginated, rolled serpiginous border and areas of ulceration spread throughout. Microscopic examination clarified the diagnosis of basal cell epithelioma. Serologic tests for syphilis were negative.

Figure 14

SQUAMOUS CELL CARCINOMA OF PERIANAL REGION vs. SYPHILITIC CHANCRE

A white woman, aged 43, has had a tender lump of the anal ring for the past month (Fig. 14). There is exquisite tenderness on cleansing after a bowel movement. Microscopic examination of the lesion shows a squamous cell epithelioma, Grade III. Serologic tests for syphilis are negative. Darkfield studies were not done because of the probability of cancer.

Figure 15 (see also Plate VIII)

MOLLUSCUM CONTAGIOSUM, ANAL vs. CONDYLOMATA LATA

A white male student, aged 23, noticed tiny lumps at the anal region (Fig. 15) when cleansing the area after a bowel movement. His roommate was found to have similar lesions on the penis. Scrapings from these lesions and the penile lesions of the roommate showed the classical bodies of molluscum contagiosum. This is not ordinarily considered to be a venereal disease. The students are homosexuals. Both were found to have negative serologic tests for syphilis.

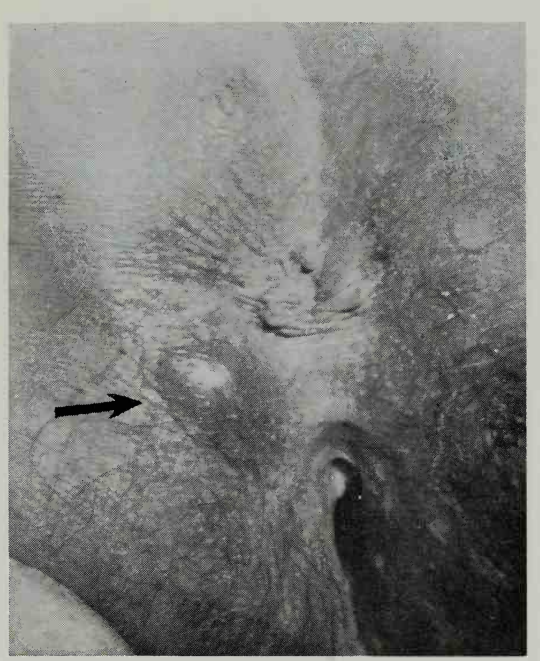

Figure 16

HIDRADENITIS SUPPURATIVA, PERIANAL vs. SYPHILITIC CHANCRE

A white woman, aged 43, developed tender raised tumors in the perianal and vulvar regions (Fig. 15). They have appeared at varying intervals for the past 6 months. When they rupture or are incised, a small amount of thick, creamy, yellowish pus exudes from them. They then usually heal gradually but occasionally drain for several months.

Cultures showed *Staphylococcus aureus*.

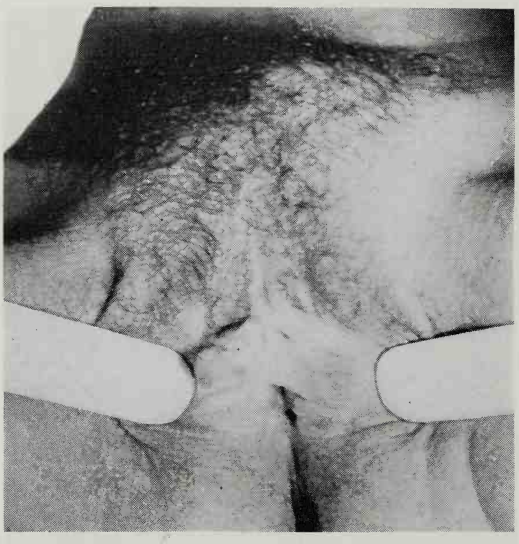

Figure 17 (see also Plate VIII)

LEUKOPLAKIA vs. MUCOUS PATCHES

A white woman, aged 53, has had itching of the vulva for the past 20 years. Three years ago she consulted a gynecologist for treatment of the itching. Examination showed thickened, whitish patches of the vulva (Fig. 17). These have gradually increased in size. Several biopsies have shown hypertrophic changes in the tissue but no evidence of carcinomatous change. Occasional fissures develop and are painful.

Treatment with the use of creams containing topical steroids gave only slight relief of itching and only slight evidence of improvement.

Vulvectomy was performed and all of the diseased tissue removed.

Figure 18 (see also Plate VIII)

LOCALIZED NEURODERMATITIS vs. LEUKPOLAKIA vs. MUCOUS PATCHES

A white woman, aged 58, had consulted a physician for treatment of an itching condition of the vulva. White patches were seen and were concluded to be leukoplakia. Vulvectomy was performed and the itching improved for several months. It then recurred and with it white patches appeared again in the scars of the operative site (Fig. 18).

The itching and the whitish patches disappeared with several weeks treatment using a topical steroid cream. It is concluded that the final diagnosis is localized neurodermatitis.

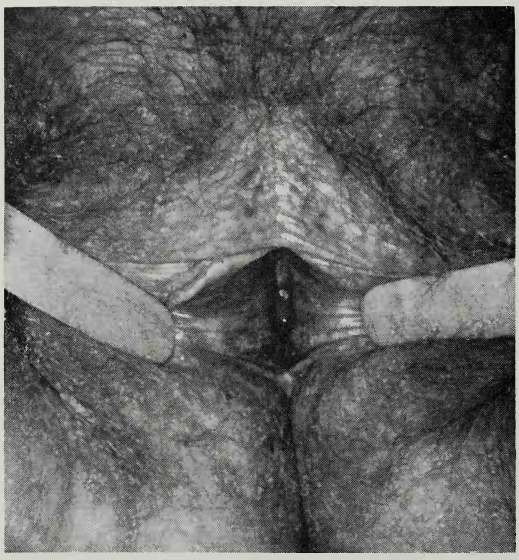

Figure 19 (see also Plate VIII)

LICHEN SCLEROSUS ET ATROPHICANS vs. MUCOUS PATCHES

A white woman, aged 46, has had itching of the vulvar region for the past 6 months. Examination of the vulva showed almost a complete disappearance of the labia minora and the labia majora were less noticeable. There is a whitish appearance of the entire vulvar area extending down and across the perineum to the perianal region producing a sort of "hour-glass" appearance.

At the right posterior portion of the inner surface of the labia minora there are hemorrhagic patches and the mucous membrane of the entire vestibule has a glazed, thin appearance.

Further examination of the general surface of the skin shows white delled papules of lichen sclerosus et atrophicans of the sides of the neck, presternal region and the inguinal folds. Some of these papules in the right inguinal folds can be seen in the above illustration.

Figure 20 Acute vulvitis (see also Plate VIII)

TRICHOMONAS VAGINALIS vs. GONORRHEA

A white housewife, aged 32, complains of itching and burning of the vulva of 2 weeks' duration. There is a profuse thick yellowish white discharge from the vagina which has been present for several months but it has been increasingly severe for the past month. There is bilateral tender inguinal lymphadenopathy.

Note above the edema of the labia minora and the vesiculation of the inner surface of the right labia majora.

Studies for the gonococcus in smears and culture were negative. Numerous Trichomonas organisms were found.

The eruption of the vulva healed when the discharge disappeared after treatment of the Trichomonas infection.

Appendix*

SUMMARY OF THE TREATMENT OF SYPHILIS

With Notes on Prognosis and Follow-up

Primary, Secondary and Early Latent Syphilis

Benzathine Penicillin G—2.4 million units total (1.2 million units in each buttock) by intramuscular injection.

or: *PAM* (Procaine Penicillin G with 2 per cent aluminum monostearate)—4.8 million units total usually given 2.4 million units at first session, as above, and 1.2 million units at each of two subsequent injections 3 days apart.

or: *Aqueous Procaine Penicillin G*—600,000 units daily for 8 days to total 4.8 million units.

or: Alternate antibiotics. (See Antibiotics.)

Prognosis: *Primary.* Lesions heal rapidly. Serologic titer falls rapidly to nonreactive.
Secondary. Lesions heal rapidly. Serologic titer reverts steadily to nonreactive, although not as rapidly as in primary syphilis.
Early Latent. (See Latent Syphilis.)

Follow-up: Clinical inspection and quantitative STS monthly for 6 months, then at 3-month intervals for 1 year. If only one spinal fluid examination is to be done, the preferred time is 12 months' post-treatment.

Note: *Report morbidity by stage to Department of Public Health. Very important this patient be interviewed for contacts. Request epidemiologic assistance from local or State health department.*

Latent Syphilis

Benzathine Penicillin G. If no spinal fluid examination is done, treatment must encompass the possibility of asymptomatic neurosyphilis. (See Late Syphilis.)
With nonreactive spinal fluid examination, 2.4 million units (1.2 in each buttock at a single session).

or: *PAM*—4.8 million units total usually given 2.4 million units at first session, and 1.2 million units at each of two subsequent injections 3 days apart.

or: *Aqueous Penicillin G*—4.8 million units total given 600,000 units daily for 8 days.

* Adapted from Syphilis—Modern Diagnosis and Management. U. S. Department of Health, Education and Welfare, Public Health Service, Publication No. 743, U. S. Government Printing Office, Washington, D. C.

or: Alternate antibiotics.

Prognosis: Serologic titer will remain stable or decline gradually, but may remain permanently reactive.

Follow-up: *Early Latent.* Same as for primary syphilis.

Late Latent. Quantitative STS at 6-month intervals for 2 years. Either a static or a falling titer may be considered satisfactory. Persistence of reactive STS alone must *not* be considered as an indication for retreatment. At least one nonreactive spinal fluid examination, either at diagnosis or before discharge.

SYPHILIS IN PREGNANCY

Treatment dependent on stage. No additional medication is necessitated by pregnancy.

Prognosis: Dependent on stage.

Follow-up: Quantitative STS in each trimester; monthly for last 3 months.

CONGENITAL SYPHILIS

Early

Under 2 years' duration, total dose of 100,000 units of PAM or aqueous penicillin per kilogram of body weight. May be given in divided doses at 2 or 3 day intervals.

or: 50,000 units of Benzathine penicillin G per kilogram of body weight total dose administered as a single intramuscular injection.

Prognosis: Lesions heal rapidly. Serologic titer descends rapidly to nonreactive.

Follow-up: Same as primary syphilis.

Late

If spinal fluid is nonreactive, treat as late latent syphilis. If spinal fluid is reactive, treat as neurosyphilis.

Note: *In treating late congenital syphilis in patients under 12 years of age, dosage of penicillin should be adjusted for age and weight.*

Note: *Interstitial keratitis usually will not respond to penicillin therapy alone. In addition to penicillin, corticosteroids (such as hydrocortisone) may be used locally in the eyes, usually with good response. Advice of an ophthalmologist should be sought.*

Note: *Management of late complications of congenital syphilis often requires individualized, specialized care.*

Prognosis: Serologic titer may be expected to remain the same or to descend slowly. Active lesions will heal, and further damage will not occur. In spinal fluid, cell count and total protein will return to normal, but titer may remain static or descend slowly.

Follow-up: If spinal fluid examination is nonreactive, quantitative serology at 6-month intervals for 2 years. If spinal was not performed initially, it should be done before patient is discharged.

If spinal fluid is reactive, quantitative serology and spinal fluid examination at 3-month intervals for first year, and at 6-month intervals for the second year. When cell count and total protein return to normal, the disease no longer is active in the spinal fluid. The spinal fluid may remain reactive for years similarly to the blood serum.

Late Syphilis (Asymptomatic and Symptomatic Neurosyphilis; Cardiovascular* and Late Benign Syphilis)

Benzathine Penicillin G—6.0 to 9.0 million units total, given 3.0 million units at 7-day intervals. (Any benefit from more than 10 million units is doubtful and has not been demonstrated.)

or: *PAM*—6.0 to 9.0 million units total, given 1.2 million units at 3-day intervals. Any benefit from more than 10 million units is doubtful and has not been demonstrated.

or: *Aqueous Procaine Penicillin G*—6.0 to 9.0 million units total, given 600,000 units daily. Any benefit from more than 10 million units is doubtful and has not been demonstrated.

Prognosis: *Asymptomatic Neurosyphilis.* Both blood and spinal titers will remain relatively stable or will decline slowly. Cell count will return to normal in spinal fluid within 6 months. Total protein will return to normal level in 6 months to 1 year.

Symptomatic Neurosyphilis. Blood and spinal fluid titers will remain stable or descend slowly. Cell count and total protein will return to normal. Destruction will be halted. Patient may show some recovery of impaired faculties as healing takes place. Where organic damage of the nervous system has progressed to destruction of nerve cells, recovery of function will not occur.

Late Benign and Cardiovascular Syphilis. Late benign lesions heal dramatically. In cardiovascular syphilis, damaged or scarred vessels and valves will not be restored to normal function.

Follow-up: *Neurosyphilis.* Quantitative serology and spinal fluid examination at 3-month intervals for the first year, and at 6-month intervals for second year. When cell count and total protein return to normal, the disease no longer is active in the spinal fluid. The spinal fluid may remain reactive for years similarly to the blood serum.

Late Benign and Cardiovascular Syphilis. Same as late latent syphilis.

Oral Medication

Oral medication is not the preferred treatment in syphilis since absorption is highly variable and patient cooperation in taking all the treatment is not always obtained.

*Note: The administration of penicillin to a person with decompensation due to cardiovascular syphilis is not an emergency, and the demand is to treat the heart first and the syphilis second. The decompensated patient should be given cardiotonic drugs and diuretics first; then, penicillin may be started in full doses without preliminary heavy metal treatment. If the patient is well compensated, penicillin treatment may be begun immediately since there appears to be no demonstrable risk from penicillin alone in these cases.

ALTERNATE ANTIBIOTICS

When penicillin sensitivity precludes use of this drug of choice, erythromycin and tetracycline are the best alternate drugs. Recommended dosage is 20 to 30 gm. of erythromycin and 30 to 40 gm. of tetracycline given over a period of 10 to 15 days.

Treatment with such alternate antibiotics must be accompanied by close follow-up of the syphilitic patient since none of these drugs has had adequate evaluation in all stages of syphilis. Spinal fluid examinations must be done as part of follow-up after this type of therapy.

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